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Cerebral Energy Metabolism: Measuring and Understanding Its Rate

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Abstract

The study of brain energy metabolism has taken second place to that of muscle ever since the dawn of this field of research. Consequently, each new discovery made using muscle tissue that advanced our understanding of the biochemistry of energy metabolic processes was attempted to be duplicated in brain tissue. It was only when the brain's high energy needs were recognized that researchers realized its vulnerability to any mishap in its energy supplies and that this vulnerability may play a role in various brain disorders. Understanding of the mechanisms by which the brain deals with energy shortage is of utmost importance in shedding light on the fundamentals of brain disorders and their potential treatment. To achieve such understanding, accurate measurement of brain energy metabolic rates is necessary. This chapter summarizes the history of the current knowledge of the biochemical processes responsible for the production of adenosine triphosphate (ATP) in the brain. It briefly reviews the various techniques used to measure cerebral metabolic rates of oxygen (CMR_{O_2}) and glucose ($\text{CMR}_{\text{glucose}}$), and elaborates on the potential of measuring the cerebral metabolic rate of lactate ($\text{CMR}_{\text{lactate}}$) to improve our understanding of brain energy metabolism.

Keywords: BOLD fMRI, cerebral metabolic rate, glucose, glycolysis, lactate, oxygen, paradigm shift, polarography

1. A short review of brain energy metabolism research

1.1 The first eight decades (1900–1980)

Most human cells produce adenosine triphosphate (ATP) via two, mostly interconnected biochemical pathways, glycolysis and mitochondrial oxidative phosphorylation. Erythrocytes (red blood cells, RBCs) produce their ATP via the glycolytic pathway alone, since they lack mitochondria. Under anaerobic conditions, the less efficient glycolytic pathway is the main source of ATP supply, since without oxygen the oxidative phosphorylation pathway cannot be maintained. Throughout the first half of the twentieth century the majority of the researchers in the field of energy metabolism made muscle their tissue of choice for the study of energy metabolism. While muscle was believed to require a great deal of energy to perform its work, the brain was assumed to be a low consumer of energy, as indicated by the following quote: *“the brain is not a seat of active combustion, and considering the very small increase in CO_2 in the torcular blood it seems to us very improbable that the temperature*

of the brain should be perceptibly greater than that of the blood” [1]. It was Tashiro [2] who was the first to demonstrate that nerve produces CO₂ and ammonia during its metabolism. By 1924, Warburg et al. [3] demonstrated that brain tissue is able to convert large amount of glucose to lactic acid, and in 1927 it was shown that nerve produces a measurable amount of heat, an amount that increases upon electric stimulation [4]. Moreover, this increase in heat production was shown to correlate with the amount of oxygen consumed. According to Holmes [5] the above finding was the necessary proof that nerve impulse is a chemical process. All the major discoveries that have led to the elucidation of the biochemical pathways of energy metabolism were made using the tissue of choice in the field i.e., muscle. Both the tricarboxylic acid cycle and the glycolytic pathways were introduced in 1937 and 1940, respectively (the reader is directed to the many detailed reviews on the topic that are available). While there is a general agreement among biochemists, physiologists and neuroscientists as to the accuracy of the mitochondrial tricarboxylic acid (TCA) cycle and the oxidative phosphorylation pathway, disagreements exist on the accuracy of the glycolytic pathway. Hence, glycolysis is the main focus of this chapter, since the original drawing of the pathway stands in conflict with various research findings of the past three decades (for more detailed reviews of this topic the reader is directed to [6, 7]). Although some research on brain energy metabolism was performed during 1920s and 1930s, it was limited to very few laboratories. Among them, that of Eric G. Holmes and Barbara E. Holmes pioneered important research in the field. The duo, who later joined by C.A. Ashford, published a series of papers [8–14] to demonstrate brain tissue production of lactate from glucose (similar to muscle metabolism), the involvement of phosphates and glycogen in this metabolism and the ability of brain tissue to oxidize lactate. Unfortunately, the latter never received neither the praise nor the scrutiny it deserved. This point is expanded upon in the next section, although it must be emphasized here that if the importance of that discovery would have been recognized at the time, our understanding of brain energy metabolism would be significantly accelerated and advanced. Nevertheless, Holmes and Ashford interpreted their finding of lactate oxidation simply as a process by which the brain rids itself of a waste product, since lactate was believed until the mid 1980s and even beyond, to be just that, a useless end-product of carbohydrate metabolism. Consequently, the research by Holmes and Ashford quickly became obscure. It would have stayed this way if not for a literature search I carried out in 2005 working on an upcoming paper that dealt with the possible role of lactate as an oxidative brain energy substrate [15]. Spending several weeks in the basement of my university medical school library (at the time most of the old literature has not yet been digitized) was an experience akin to treasure hunt, an experience I still cherish today. Discovering Holmes and Ashford’s papers in 75-year old, dust-covered, heavy volumes of the Biochemical Journal was almost as exciting as conducting our own research [16]. Three years prior to the publication of the latter on brain energy metabolism, Brooks published his controversial work on muscle energy metabolism [17]. His proposal that skeletal muscle both produces and consumes lactate met with major objections because such consumption would require lactate to be a mitochondrial substrate, which requires the existence of lactate dehydrogenase in mitochondria (mLDH), an enzyme his detractors strongly insisted does not exist. Schurr and colleagues demonstrated *in vitro* that brain tissue is capable of maintaining normal neuronal function when lactate is the sole oxidizable energy substrate [16]. Skeptics of this finding argued that the phenomenon does not occur *in vivo* and even if it does, lactate cannot replace glucose as the obligatory energy substrate in brain [18]. And thus began a long-lasting debate on the validity of these findings and the potential importance of lactate as an oxidative substrate of energy metabolism in brain and elsewhere. **Figure 1** is an illustration

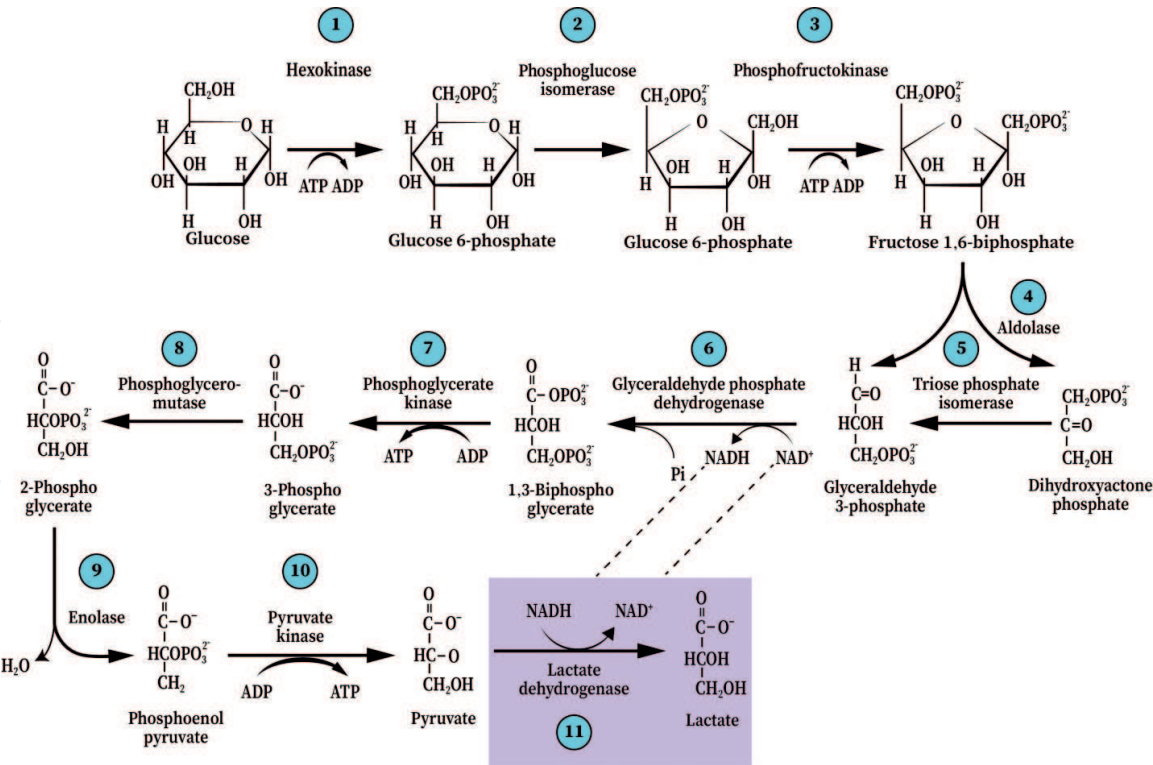


Figure 1.
The classical description of the 10 enzymatic steps of aerobic glycolysis, the pathway that converts glucose to pyruvate with a net production of two molecules of ATP and two molecules of pyruvate, its end-product and the substrate of the mitochondrial tricarboxylic acid (TCA) cycle. Under anaerobic conditions, an eleventh enzymatic step occurs where pyruvate is converted to lactate, which becomes the glycolytic end-product under these conditions.

of the glycolytic pathway as it has been conceived and taught everywhere since 1940. This concept has been based on an initial assumption, made not by those who proposed the original reaction sequence of the glycolytic pathway, but by Krebs and Johnston, who proposed the reaction sequence of the mitochondrial TCA cycle [19]. The latter postulated that pyruvate is the substrate of that cycle and assumed that glycolysis could be its origin. Such an assumption, when made by a leading scientist of the status Krebs had achieved, was persuasive enough to compel Gustav Embden, Otto Meyerhof, and Jakub Karol Parnas to decide that pyruvate is the end-product of aerobic glycolysis and the substrate of the TCA cycle. Hence, for almost eight decades the glycolytic pathway has been described as one that has two possible outcomes, an aerobic one, which ends with pyruvate and an anaerobic one that ends with lactate (**Figure 1**). Every biochemistry textbook published from the 1940s on, every biochemistry, physiology or neuroscience course being taught at any level and every online search, all display this very description of the glycolytic pathway. That, despite ample research data that clearly refute this dogmatic paradigm.

1.2 The last four decades (1980–2018)

As indicated above, questions as to the correctness of the old description of glycolysis began to appear in the late 1980s. The lactic acidosis hypothesis of delayed neuronal damage [20] had a strong following at the time. This hypothesis postulated that lactate accumulation in the ischemic brain is the cause of delayed neuronal damage, damage observed after a recovery from the original ischemic insult had occurred. The popularity of this hypothesis was so strong that any insinuation that lactate could be anything but a menacing factor in cerebral ischemia aroused great skepticism. Consequently, when Fox et al. [21] published

a study, which indicated that neural activation does not require an increase in energy supply and is supported by a mere non-oxidative glucose utilization (“anaerobic” glycolysis), they met with both doubt and a degree of cynicism. Almost simultaneously, Schurr et al. [16] published their findings demonstrating that neuronal function *in vitro* can be supported by lactate as the sole oxidizable energy source. These findings were met with even greater doubt and cynicism, some of which continues to this day. The past 30 years have seen the field of brain energy metabolism grow by leaps and bounds as new technologies and techniques enable scientists to explore, measure and interpret their findings more accurately. Nevertheless, such interpretations depend on the accuracy of our knowledge and understanding of the basic pathways and processes of energy metabolism. The ongoing debate about the correct paradigm of glycolysis, as highlighted by Schurr and Gozal [22] and many of the papers within this Research Topic volume, clearly indicates that such accuracy and understanding are still to be achieved. To illustrate this point consider on one hand, the conclusion of Fox et al. [21] regarding the very low increase in energy demand upon neural stimulation, demand that can be easily answered by non-oxidative glycolysis i.e., glucose consumption unaccompanied by oxygen consumption, while on the other hand, the conclusion by Hyder et al. [23] that activated neural tissue exhibits an increase in energy production, which is fully oxidative i.e., the ratio of oxygen to glucose for this increase is 6:1. Could these completely opposing conclusions be explained by differences in the methodologies used in the two studies (the former made use of ^{18}F -2-fluoro-2-deoxy-D-glucose to measure glucose uptake and $^{15}\text{O}_2$ to measure oxygen consumption, while the latter made use of blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI))? Or maybe the measurements by both methods are correct, but their interpretation has relied on assumptions that emanated from older, dogmatic concept?

To answer this question, one must consider the mounting evidence supporting a paradigm shift in our comprehension of the glycolytic pathway [24]. The shift entails redrawing the glycolytic pathway as one consisting of 11 steps, beginning with glucose as its substrate and ending with lactate as its end-product, independent of the presence or absence of oxygen. From its inception, distinguishing between aerobic and anaerobic glycolysis was based not on specific evidence that the two pathways exist and produce two different products, pyruvate and lactate, respectively. That separation was an attempt by the pathway’s elucidators to somehow fit it into, what they concluded, is an outcome that produces pyruvate as its main end-product since they accepted Kreb’s suggestion that this monocarboxylate is the substrate of the TCA cycle. It must have been relatively easy to accept that suggestion considering lactate’s negative reputation [6]. Hence, the glycolytic pathway should be considered one, uninterrupted chain of biochemical reactions that begins with glucose and ends with lactate (**Figure 1**). Accordingly, its last reaction (number 11), the reduction of pyruvate to lactate by the cytosolic lactate dehydrogenase (cLDH), plays a crucial role in keeping this pathway’s cyclical nature operational as it provides a continuous supply of NAD^+ . If pyruvate was the glycolytic end-product, NAD^+ would have to be imported from other sources and locations, a proposition that has offered a somewhat shaky resolution (see [25] and references within). This, of course, is not the only factor that justifies a paradigm shift. There are numerous studies published over the past two decades demonstrating the presence of lactate dehydrogenase in mitochondria (mLDH), an enzyme that converts lactate to pyruvate [26–32]. Brooks et al. [33] also demonstrated the presence of monocarboxylate transporter 1 (MCT1) in mitochondria, the transporter that is responsible for the transport of lactate along its gradient from the cytosol to the mitochondrion. Havel et al. showed that in blood and in other tissues the

ratio lactate/pyruvate is >10 , a value that is not consistent with the assumption that pyruvate is the glycolytic end-product [34]. Moreover, the proposal that aerobic glycolysis ends with pyruvate does not meet the known standard free-energy (ΔG^0) change of the reaction pyruvate \rightarrow lactate, which is -6.0 kcal/mol, a value indicating that this reaction should proceed independently of the presence or absence of oxygen. In other words, glycolysis, whether aerobic or anaerobic, should always end up with lactate. **Figure 2A** demonstrates the free energy change profile of aerobic glycolysis that ends with the reaction phosphoenolpyruvate \rightarrow pyruvate, although the potential free-energy change of the conversion pyruvate \rightarrow lactate (**Figure 2B**, anaerobic glycolysis) determines that glycolysis should end with lactate regardless of the oxygenation condition (**Figure 2C**). Last but not least, the reaction equilibrium of cLDH is tilted heavily in the direction of lactate production, which makes it unlikely for lactate to be converted back to pyruvate by that cytosolic enzyme. In contrast, the reaction equilibrium of mLDH tilts in the direction of lactate oxidation to pyruvate [35, 36].

The above points support the proposed paradigm shift in the glycolytic pathway [24], where lactate, not pyruvate, is its end-product and the oxidative mitochondrial substrate for the TCA cycle. Accordingly, is measuring the cerebral metabolic rates of oxygen (CMR_{O_2}) and glucose ($\text{CMR}_{\text{glucose}}$) sufficient in providing an accurate picture of brain energy metabolism during rest or activation, in health or disease? If lactate is an oxidative energy substrate, should not $\text{CMR}_{\text{lactate}}$ also be measured in order to have a more complete account of cerebral energy metabolism? How would the measurement of $\text{CMR}_{\text{lactate}}$ contribute to our understanding of the brain's ability to handle its energy demands under those conditions?

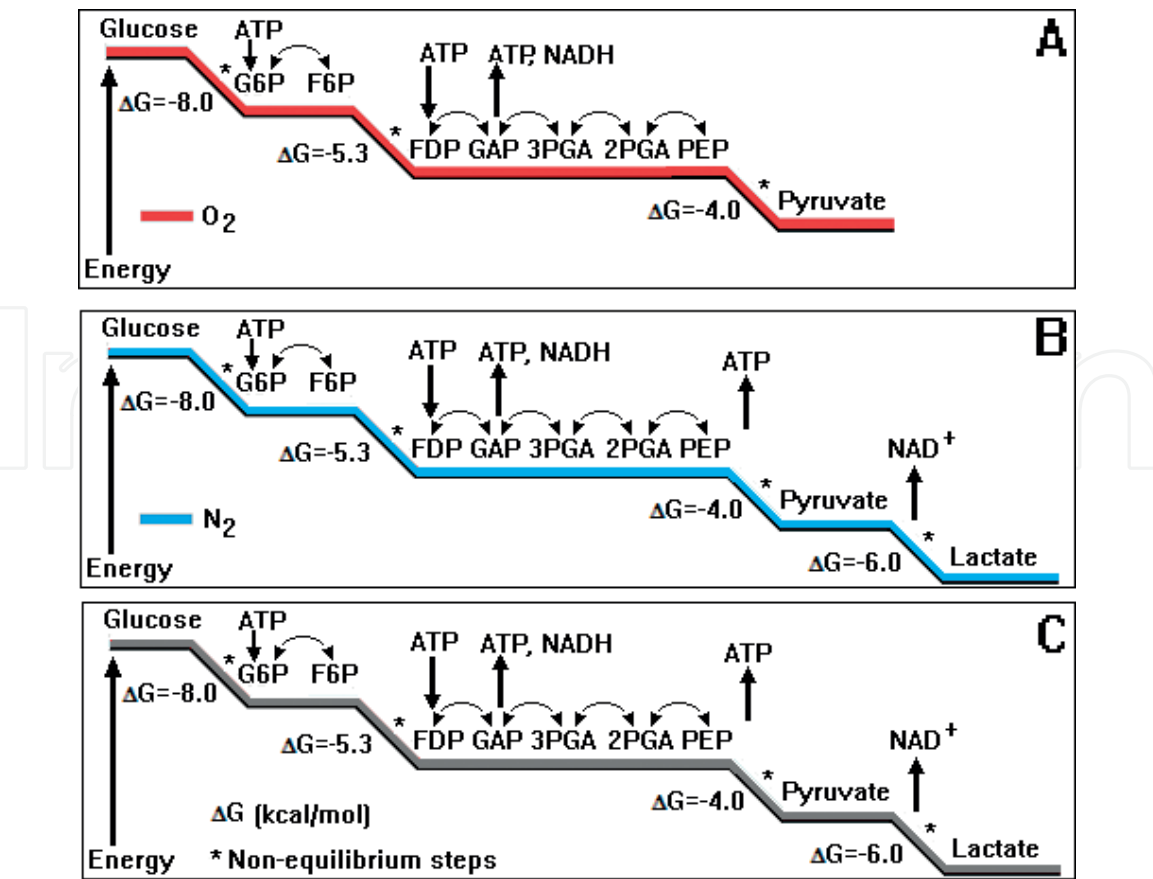


Figure 2. A schematic illustration of the potential free-energy change profile of aerobic (A) and anaerobic glycolysis (B). The potential free-energy change of the reaction pyruvate \rightarrow lactate dictates that it should proceed regardless of the oxygenation conditions (C).

2. Measurement of cerebral energy metabolic rates

At the basis of each technology designed to measure the rate of brain energy metabolism is the idea that measuring the consumption rate of the main two substrates of glycolysis and mitochondrial respiration, glucose and oxygen (O_2), should provide a complete picture of the brain's energy use. Theoretically, under normal conditions, each glucose molecule that enters the glycolytic pathway requires six molecules of oxygen to be fully oxidized via the mitochondrial TCA cycle and the electron transport chain. Thus, simultaneous measurements of glucose and oxygen consumption during rest or activation supposedly produces accurate estimate of the energy needs for the brain region under observation. However, the ratio $CMR_{O_2}/CMR_{glucose}$ values calculated are often significantly smaller than the expected 6/1. Such discrepancies have attributed to other glucose-consuming reactions not accompanies with oxygen consumption. Consequently, it has been a common understanding that a value of $CMR_{O_2}/CMR_{glucose} < 6$ indicates that a partial non-oxidative glucose consumption. The smaller the value of $CMR_{O_2}/CMR_{glucose}$, the greater is the non-oxidative consumption of glucose. This understanding makes sense when one assumes that a fully coupled glycolytic-mitochondrial respiratory apparatus should produce a $CMR_{O_2}/CMR_{glucose}$ value of 6 and an uncoupled apparatus (non-oxidative) should produce a $CMR_{O_2}/CMR_{glucose}$ value of ~ 0 .

As indicated above, myriad techniques and technologies have been developed during the past six decades to measure both CMR_{O_2} and $CMR_{glucose}$. To measure cerebral energy metabolism *in vivo* one can analyze chemical changes in the blood entering and exiting the brain and/or in the cerebrospinal fluid. Of course, brain tissue samples can also be taken for analysis before and after physiological activity, although this approach would lend itself only to experimental animals. The introduction of radioisotopes to the analytical techniques of brain metabolic activity has greatly improved their speed and accuracy. Radioisotopes allow not only the tracing of end-products of cerebral metabolism, but also the detection of intermediates of that metabolism. Nevertheless, these techniques have their own drawbacks, including the need to sacrifice the animal under study only to receive a single measurement which provides mainly a qualitative value. A quantitative measurement is frequently confounded by compartmentation and its misinterpretation thereof. One of the most reliable techniques to measure oxygen consumption is the polarographic technique, which allows the determination of oxygen concentration via the measurement of the partial oxygen pressure (PO_2) locally. Continuous measurements over a period of time when brain activity (EEG) is monitored, demonstrated a correlation between increased activity and decreased tissue oxygen level. The development of oxygen microelectrodes has afforded a more accurate localization of such measurements.

In principle, CMR can be expressed as: $CMR = CBF (A - V)$.

where $(A - V)$ is the difference in concentration in arterial and cerebral venous blood, CBF is the rate of cerebral blood flow in volume of blood per unit time, a CMR (cerebral metabolic rate) is the steady state of utilization or production of a substance by the brain [18]. This equation is the foundation on which quantitative CMR studies *in vivo* have been conducted. Since the normal brain consumed approximately 20% of the total body oxygen consumption to maintain its functionality and structure, it is clear that any interruption in this high demand for oxidative energy metabolism could have far reaching survivability consequences. Clearly, a non-oxidative energy metabolism (glycolysis) is incapable of answering the high energy demands of the brain. That a stimulated brain has still higher energy demands than the resting one would be an inevitable conclusion. Hence, when studying the energy demands of a specific activated brain region, such activation is expected to produce

an increase in both CMR_{O_2} and $\text{CMR}_{\text{glucose}}$. Consequently, when Fox et al. published their study under the title “Nonoxidative glucose consumption during focal physiologic neural activity” [21] they stirred a small tempest among scientists in the community that studies cerebral blood flow and metabolism. These investigators employed ^{18}F -labeled 2-fluoro-2-deoxy-D-glucose to measure $\text{CMR}_{\text{glucose}}$, a method originally developed over a decade earlier [37], and ^{15}O -labeled molecular O_2 to measure CMR_{O_2} . They demonstrated that transient increases in neural activity elevated glucose tissue uptake in excess of that consumed by oxidative metabolism. They concluded their findings to indicate that stimulated brain activity requires significantly less energy than previously thought. Also, since they measured a corresponding increase in CBF along with the increase in glucose consumption, the investigators argued that this increase is for purposes other than oxidative metabolism. These conclusions stemmed from the prevailing postulate that over 90% of resting brain’s glucose consumption is oxidative and less than 5% of that consumption ends in glycolytic lactate production. Since the oxidative consumption of one molecule of glucose produces approximately 36 molecules of ATP, while the glycolytic consumption of one molecule of glucose produces only 2 molecules of ATP, one can easily appreciate how oxidative consumption of glucose is responsible for 90% of the resting brain ATP production. Hence, the finding by [21] that brain stimulation increased glucose consumption without a corresponding increase in oxygen consumption unsettled the established understanding according to which increased brain activity must be accompanied by a corresponding increase in energy supply. This seminal paper was originated from the laboratory of Marcus Raichle, a laboratory that has become a leading center for functional brain imaging [38]. Imaging technologies such as X-ray computed tomography (CT), positron emission tomography (PET), near-infrared spectroscopy (NIRS) and magnetic resonance imaging (MRI) are the main techniques available for the measurement of brain energy metabolism during rest and activity. The most popular technology for this purpose today is the blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI), which was developed by [39]. BOLD fMRI measures changes in blood oxygenation in relation to brain activity, although that relationship is somewhat ambiguous, since it is not accompanied by a direct neural activity measurement such as that allowed by electrophysiology. When the latter is combined with direct oxygen concentration measurements, using an oxygen microelectrode (polarography), a higher resolution than BOLD fMRI can be achieved [40]. Besides tissue oxygen measurements using microelectrodes, tissue glucose and lactate concentrations can also be assessed using specific microelectrodes (sensors). Of course, this approach does not lend itself for regular use in humans, however, for the purpose of *in vivo* studies in experimental animals, the approach proved itself to be very useful and an eye opener.

In this respect, Hu and Wilson [41] studied the coupling of a temporary local energy pool to neuronal activity in the rat brain (**Figure 3**). They were the first to combine the use of three separate rapid response sensors (microelectrodes) to measure tissue oxygen, glucose and lactate concentrations. The investigators placed them in the dentate gyrus of the rat hippocampus, observing how they fluctuate in response to 10 consecutive electrical stimulations of the perforant pathway (each stimulus lasted 5 s and applied every 2 min). Their results were analyzed by Schurr and Gozal [36] (**Figure 3**). A literature search shows that Hu and Wilson’s interpretation of their findings has its supporters [15, 42–47] and detractors [48–50]. The former group argued that these findings are strengthening the concept that lactate is the energy substrate that is utilized oxidatively upon neuronal activation. The latter group disagreed with this conclusion. Schurr [24] further analyzed the results of Hu and Wilson [41] beyond an earlier analysis [36]. The more recent analysis was prompted for two reasons. First, two decades have passed since the publication

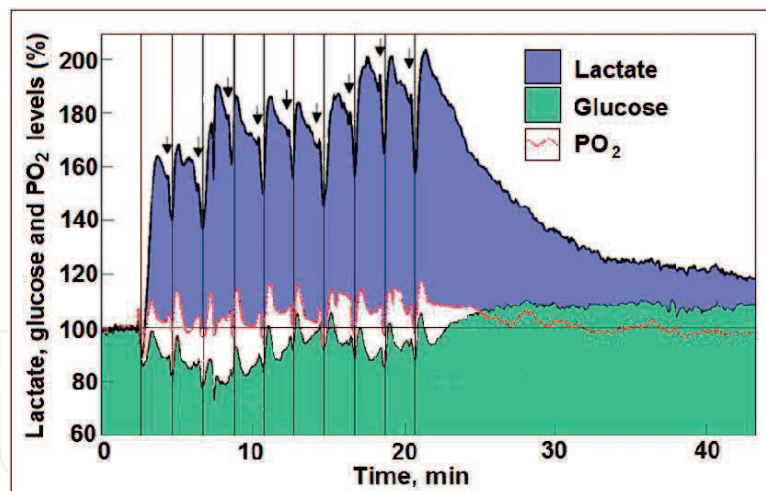


Figure 3.

Profiles of time course and dynamic relationships of local extracellular lactate, glucose, and PO_2 levels in the rat hippocampal dentate gyrus during a series of 5 s electrical stimulations (arrows) of the perforant pathway at 2 min rest intervals (reproduced with permission from Hu and Wilson, copyright 1997, Blackwell, Oxford). The changes in the mean concentration of glucose were always in opposite direction to the changes in mean lactate concentration. The vertical lines were drawn to indicate the simultaneous dip in all three analytes in response to each of the electrical stimulations. For additional details see [41] from where the figure and the legend have been reproduced with permission and [36].

of the paper by Hu and Wilson [41], a period in which numerous studies added much support to the idea that lactate is a mitochondrial oxidative energy substrate. Second, many other studies on cerebral energy metabolism continue to conclude that neural activity is supported by “anaerobic” glycolysis and not by oxidative utilization of glucose, while ignoring the possibility that such activity may be supported by oxidative utilization of lactate.

3. Lactate cerebral metabolic rate and the importance of its measurement

When the results of the study by Hu and Wilson [41] were analyzed before [36], the analysis showed that upon a series of 10 stimulation of the rat hippocampal perforant pathway a steady glucose consumption was accompanied by a gradual increase in lactate consumption. Considering the conclusion of Fox et al. [21] that aerobic glycolytic ATP production is sufficient to answer the energy needs of activated neural tissue, one could assume that it should be sufficient to provide the energy needs of the stimulated hippocampal dentate gyrus. In addition, this analysis points out that if the conclusion of Fox et al. [21] is correct, the energy needs of the activated dentate gyrus declined with each stimulation or stayed the same at a very low level of ATP production (0.8–0.3 mM). However, if lactate oxidative consumption is postulated to be responsible for the ATP production that sustains the energy needs of the stimulated tissue, the increased lactate consumption with each consecutive stimulation signals a concomitant increased ATP production. The calculation shows that the response to the first stimulation produced 3 mM ATP, while the response to the last stimulation produced almost 11 mM (**Figure 4**).

The more recent analysis [24] also indicates that the increased levels of tissue lactate following each stimulation [41] could not be produced from the glycolytically metabolized glucose (**Figure 5**). Hence, this additional lactate had to be originated from other sources i.e., the surrounding tissue or glycogen stores [50]. As was shown by Hu and Wilson [41] (**Figure 3**), a larger amount of lactate was consumed during each consecutive stimulation, while a smaller amount of glucose was

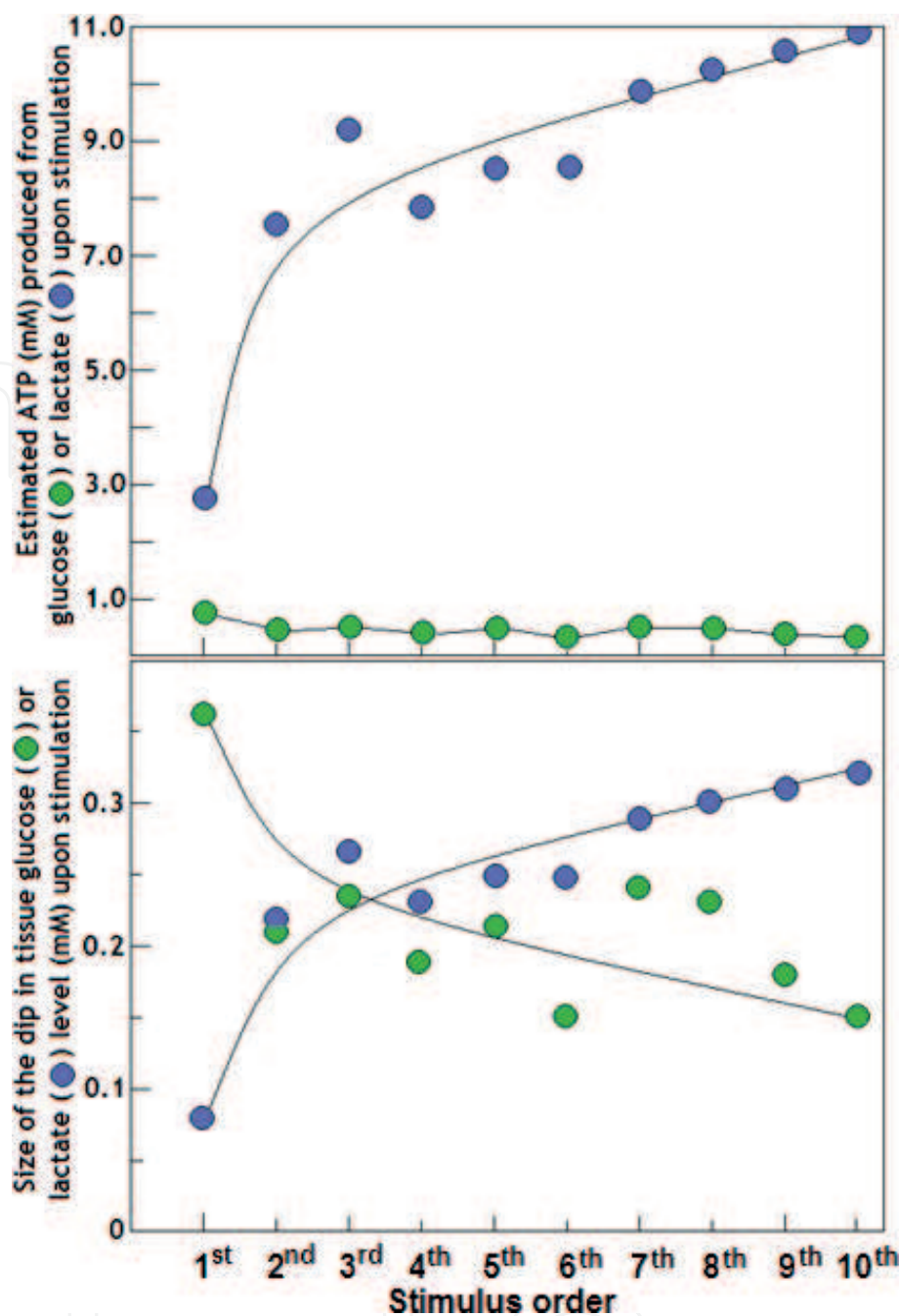


Figure 4. Time course of changes in the amplitude of the dip in tissue glucose and lactate levels in the rat hippocampal dentate gyrus after each of the 10 electrical stimulations applied to the perforant pathway at intervals of 2 min (bottom panel). The amplitude of each dip (in mM) was calculated from the Hu and Wilson [41] as reproduced in Figure 3. The upper panel represents the estimated ATP amount produced based on the size of the dip (in mM) in tissue glucose and lactate levels as shown in the bottom panel. The estimated ATP levels were calculated as follows: the glucose measured dip (in mM) was multiplied by 2, the net production of 2 moles ATP from each mole of glucose metabolized glycolytically; the lactate measure dip (in mM) was multiplied by 34, the net formation of 34 moles of ATP for every 2 moles of lactate (form glycolytically from 1 mole of glucose) metabolized via the mitochondrial TCA cycle and the oxidative phosphorylation chain.

consumed. Moreover, following each stimulation, except the first one, the lactate level measured exceeded the level expected from the amount of glucose consumed glycolytically i.e., two moles of lactate from one mole of glucose. Following the second stimulation, the tissue ratio of lactate to glucose was 3.95 and by the 10th stimulation this ratio increased to 8.33 (Figure 5). Meanwhile, oxygen tissue levels dipped and rose as expected during and after each stimulation, respectively, signaling that the electrical stimulation evoked an oxidative consumption of substrate. Initially, glucose and lactate were oxidatively consumed at equal amounts however,

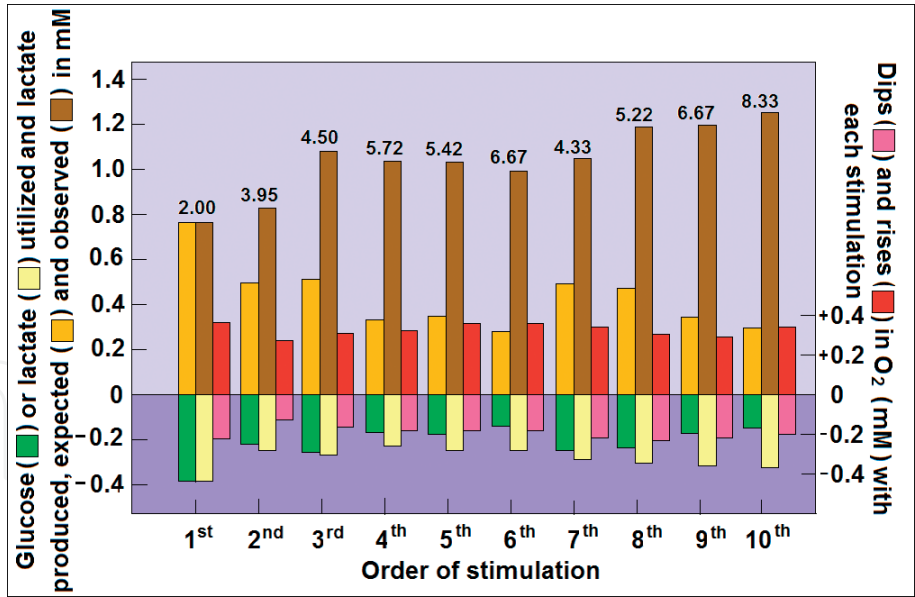


Figure 5. The local extracellular glucose, lactate and O_2 levels in a rat hippocampal dentate gyrus during a series of 5 s electrical stimulations of the perforant pathway at 2 min rest intervals and the dynamic relationship between them. Glucose, lactate and O_2 concentrations were calculated from their dips and rises as measured by Hu and Wilson [41] using rapid response sensors. The numerical values posted above the columns representing the rises in glucose and lactate post-stimulation are the calculated ratios between the two. For additional details see Figure 3 and [36].

from the second stimulus onward more lactate than glucose was consumed (Figure 5). The oxygen level as measured by Hu and Wilson [41] fluctuated with a dip upon stimulation and a sharp rise upon its cessation (Figure 3). The fast rise can be interpreted as evidence that ample oxygen was available if and when needed. This rise also indicates that the tissue was well oxygenated during the duration of the experiment. Considering that one mole of lactate consumes three moles of oxygen for its full oxidation as compared to six moles of oxygen consumed by glucose for its full oxidation, if lactate, rather than glucose, is the main oxidative energy substrate during neural tissue activation, the expected ratio $CMR_{O_2}:CMR_{lactate}$ should not exceed 3:1. Therefore, it is reasonable to presume that during neural activation, when lactate oxidation is a major supplier of the ATP necessary to support said activation, the ratio $CMR_{O_2}:CMR_{glucose}$ should be considerably lower than 6:1. Obviously, most, if not all, studies aimed at measuring cerebral metabolic rates postulate that the ratio $CMR_{O_2}:CMR_{glucose}$ measured or calculated should approach 6 [23]. The conclusions of Fox et al. [21] are in complete disagreement with the measurements and calculations of Hyder et al. [23]. While the former concludes an almost complete uncoupling between glucose and oxygen consumption by activated neural tissue, the latter asserts the maintenance of full coupling between glucose and oxygen consumption during neural activation. In both studies [21, 23] the interpretation of the results is based entirely on the original, dogmatic paradigm of glycolysis according to which aerobic glycolysis ends with pyruvate, the assumed substrate of the mitochondrial TCA cycle.

The *in vivo* measurements performed by Hu and Wilson [41] of both glucose and lactate concentrations before, during and post electrical stimulation provide much support to the proposal that lactate plays a major role in oxidative energy metabolism of the activated neural tissue. The relatively small dips and rises in O_2 levels in response to the electrical stimulations, as measured polarographically, should be given additional consideration. First, the spatial and temporal resolutions provided by polarographic measurement of O_2 compared to BOLD fMRI measurements allow for a better characterization of the time-course of oxygen responses [40].

Hyder et al. [23] used BOLD fMRI and the measurements used by Fox et al. [21] were even more cumbersome, involving the use of $[^{15}\text{O}]\text{H}_2\text{O}$, $[^{15}\text{O}]\text{O}_2$ and $[^{15}\text{O}]\text{CO}_2$.

While BOLD fMRI estimates yielded a $\text{CMR}_{\text{O}_2}:\text{CMR}_{\text{glucose}}$ ratio value of 6:1, the ^{15}O measurements produced a ratio value of 0.4:1. These completely opposing outcomes make one wonder whether or not the measurements performed using these two methods and the calculated values of CMR_{O_2} they produced truly reflect the changes in the consumption of molecular oxygen upon neural activation. Could the direct measurements of CMR_{O_2} , $\text{CMR}_{\text{glucose}}$ and $\text{CMR}_{\text{lactate}}$ done by Hu and Wilson [41] along with the indirect ones made by Fox et al. [21] and Hyder et al. [23], be reconciled such that a better picture of cerebral metabolic rates of activated neural tissue can be visualized? It is widely agreed that over 90% of the normal brain's energy production originates from glucose oxidation [21, 51]. The normal glucose concentration in the brain is ~ 2 mM and its normal lactate concentration is about half of that of glucose. Thus, it is safe to postulate that the normal resting brain is supplied with ample amounts of oxygen to continuously oxidize more than 90% of the brain glucose. However, glucose supplies to the normal brain are limited (only 40% of normal blood glucose level). Consequently, the increased rate of CBF along with the increased consumption of glucose upon activation [21, 23, 52] should supply all the oxygen necessary to match the increased demand, in contrast to the limited supplies of glucose. Low resolution techniques for the measurements of oxygen concentrations are unable to detect local fluctuations accurately if at all, which could explain why Fox et al. [21] reached the conclusion regarding the very low oxygen consumption during neural activation. Nonetheless, their conclusion that the energy demands of activated neural tissue are being met through glycolytic ATP production is most likely incorrect. In other words, undetectable or slightly detectable dip in tissue oxygen level upon activation is not necessarily an indication that oxygen is not consumed. The higher resolution of oxygen measurement afforded by polarography exemplifies the fact that local oxygen levels dipped upon stimulation and overshot upon its cessation ([41]; **Figures 3 and 4**). Although local fluctuations in tissue oxygen levels were evident, its overall tissue concentration did not significantly change and may even have risen somewhat above its baseline level. In contrast, both glucose and lactate levels were changed significantly from their baseline levels [24, 36, 41] (**Figures 3–5**). The fluctuations between lactate and oxygen were highly synchronized, indicating that lactate is being oxidized upon tissue activation. During the 20 min following the 10th stimulation, the tissue level of both oxygen and glucose climbed above the baseline level, while the high level of lactate gradually declined ([41]; **Figure 3**). These shifts seem to indicate that upon cessation of stimulation, as the tissue is recovering from activation and high energy demands, lactate becomes the preferred oxidative energy substrate, sparing glucose. That the cerebral tissue would prefer lactate over glucose, especially when the former is abundant, is reasonable, considering the fact that lactate oxidative mitochondria. Consequently, the increased rate of CBF along with the increased consumption of glucose upon activation [21, 23, 52] should supply all the oxygen necessary to match the increased demand, in contrast to the limited supplies of glucose. Low resolution techniques for the measurements of oxygen concentrations are unable to detect local fluctuations accurately if at all, which could explain why Fox et al. [21] reached the conclusion regarding the very low oxygen consumption during neural activation. Nonetheless, their conclusion that the energy demands of activated neural tissue are being met through glycolytic ATP production is most likely incorrect. In other words, undetectable or slightly detectable dip in tissue oxygen level upon activation is not necessarily an indication that oxygen is not consumed. The higher resolution of oxygen measurement afforded by polarography exemplifies the fact that local oxygen levels dipped upon stimulation and overshot upon its cessation (**Figures 3 and 4** and [41]). Although local fluctuations in tissue

oxygen levels were evident, its overall tissue concentration did not significantly change and may even have risen somewhat above its baseline level. In contrast, both glucose and lactate levels were changed significantly from their baseline levels (**Figures 3–5** and [24, 36, 41]). The fluctuations between lactate and oxygen were highly synchronized, indicating that lactate is being oxidized upon tissue activation. During the 20 min following the 10th stimulation, the tissue level of both oxygen and glucose climbed above the baseline level, while the high level of lactate gradually declined (**Figure 3** and [41]). These shifts seem to indicate that upon cessation of stimulation, as the tissue is recovering from activation and high energy demands, lactate becomes the preferred oxidative energy substrate, sparing glucose. That the cerebral tissue would prefer lactate over glucose, especially when the former is abundant, is reasonable, considering the fact that lactate oxidative utilization, in contrast to glucose, does not involve ATP investment prior to its utilization by mitochondria.

4. CMRs measurements and their possible implications in brain disorders

Energy metabolic interruptions are at the basis of several brain disorders and measuring CMRs of patients inflicted by such brain disorders can offer a potentially better diagnosis and treatment. Measurement of CMR_{O_2} and $\text{CMR}_{\text{glucose}}$ have been performed regularly in numerous studies of cerebral ischemia in an effort to better understand the mechanisms of neuronal ischemic damage. $\text{CMR}_{\text{glucose}}$ measurement has been used in studying obsessive-compulsive disorder, mood disorder and depression, where the main aim is to follow changes in glucose metabolism in specific brain regions believed to be involved in these disorders. Other brain disorders where glucose metabolic rate has been measured include amyotrophic lateral sclerosis, Alzheimer's disease, epilepsy, Parkinson's disease and Huntington's disease. The purpose behind the measurement of glucose cerebral metabolic rate when investigating diseases and disorders is usually to identify brain regions that are involved in a given disorder or disease, not to investigate how energy metabolism is being affected by the disease or the disorder. Also, the energy metabolic rates of brain tumors have received great attention due to the unique energy requirements of these tumors. Nevertheless, cerebral ischemia and traumatic brain injury (TBI) are the two disorders for which measurements of CMR_{O_2} and $\text{CMR}_{\text{glucose}}$ are most abundant. The results of these measurements prompted proposals both for treatments and mechanisms of neuronal damage due to these insults. The most heralded hypothesis attempting to explain delayed neuronal cerebral ischemic damage [20] known as the lactic acidosis hypothesis, postulated the accumulation of lactic acid as the cause of that damage. Consequently, physicians dealing with stroke patients were encouraged to control blood glucose levels in these patients, based on the assumption that the higher the glucose level during cerebral ischemia, the higher the level of lactic acid produced and the damage it causes. The lactic acidosis hypothesis was discarded, although the practice of controlling the blood glucose level of stroke patients remained. To this end, lactate was shown to support neuronal recovery post-ischemia *in vitro* [53–55]. Moreover, higher glucose level pre-ischemia (hypoxia) appear to improve neuronal recovery post-ischemia *in vitro* [56] and any exacerbation of neuronal damage due to pre-ischemic hyperglycemia was shown to be induced by increased levels of stress hormone [57]. Similarly, experimental [58] and clinical studies [59–66] over the past two decades indicate that lactate supplementation after TBI improves post-injury outcome. Measurement of $\text{CMR}_{\text{lactate}}$ could greatly enhance our understanding of the role that this monocarboxylate plays in these two brain disorders.

5. Conclusions

A paradigm shift of a scientific model should, naturally, result in reconsideration of hypotheses and concepts that have been formulated on its foundation prior to its shift. The understanding of cerebral metabolic rates of energy substrates during rest and activation of neural tissue, the use of the method best suited for the measurement of these rates and the interpretation of the results have always relied on two fundamental assumptions. First, cerebral energy metabolism includes the obligatory glycolytic breakdown of glucose to pyruvate and the utilization of the latter by the mitochondrial TCA cycle and the electron transport chain with oxygen as its final receptor. Second, the activation of cerebral tissue is sustained by an increase in ATP production and therefore an increase in the consumption of glucose and oxygen. Two seminal papers that were published almost simultaneously [16, 21] have forced biochemists, and especially neuroscientists, to reassess these two basic postulates. The paper by Fox et al. [21] has perplexed many with its conclusion that the energy requirements of activated neural tissue are minimal and can be fulfilled by the glycolytic pathway alone (glucose \rightarrow lactate + 2ATP). The paper by Schurr et al. [16] provoked great skepticism upon demonstrating that neural tissue can function and be activated when lactate is its sole oxidative energy substrate (lactate + 3O₂ + mitochondria \rightarrow pyruvate \rightarrow TCA cycle \rightarrow 3CO₂ + 3H₂O + 17ATP). While the proposal that lactate is a suitable oxidative energy substrate had faced strong skepticism for many years, it has gained greater support over the past three decades. The proposal that glycolysis could be served as the sole supplier of energy for the activated neural tissue still divides scientists working in this field. By accepting the proposed paradigm shift of glycolysis [24] and its application in the interpretation of the results obtained by Fox et al. [21], Hyder et al. [23, 67], Hu and Wilson [41] and many others, a scenario can be drawn where lactate is supplementing most if not all the energy requirements of activated neural tissue. The data and the line of reasoning presented here strongly argue against the conclusion that these energy requirements are solely fulfilled by glycolysis. Future studies of activated cerebral metabolic rates should include, along with the measurements of CMR_{O₂} and CMR_{glucose}, the measurement of CMR_{lactate}. Resolving the existing debated issues of cerebral energy metabolism is paramount for our better understanding the many brain diseases and disorders. Hopefully, this chapter provides a possible resolution of some of these issues.

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