

A “Lactatic” Perspective on Metabolism

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ABSTRACT

GLADDEN, L. B. A “Lactatic” Perspective on Metabolism. *Med. Sci. Sports Exerc.*, Vol. 40, No. 3, pp. 477–485, 2008. The cell-to-cell lactate shuttle was introduced in 1984 and has been repeatedly supported by studies using a variety of experimental approaches. Because of its large mass and metabolic capacity, skeletal muscle is probably the major component of the lactate shuttle in terms of both production and consumption. Muscles exercising in a steady state are avid consumers of lactate, using most of the lactate as an oxidative fuel. Cardiac muscle is highly oxidative and readily uses lactate as a fuel. Lactate is a major gluconeogenic substrate for the liver; the use of lactate to form glucose increases when blood lactate concentration is elevated. Illustrative of the widespread shuttling of lactate, even the brain takes up lactate when the blood level is increased. Recently, an intracellular lactate shuttle has also been proposed. Although disagreements abound, current evidence suggests that lactate is the primary end-product of glycolysis at cellular sites remote from mitochondria. This lactate could subsequently diffuse to areas adjacent to mitochondria. Evidence is against lactate oxidation within the mitochondrial matrix, but a viable hypothesis is that lactate could be converted to pyruvate by a lactate oxidation complex with lactate dehydrogenase located on the outer surface of the inner mitochondrial membrane. In another controversial area, the role of lactic acid in acid–base balance has been hotly debated in recent times. Careful analysis reveals that lactate, not lactic acid, is the substrate/product of metabolic reactions. One view is that lactate formation alleviates acidosis, whereas another is that lactate is a causative factor in acidosis. Surprisingly, there is little direct mechanistic evidence regarding cause and effect in acid–base balance. However, there is insufficient evidence to discard the term “lactic acidosis.” **Key Words:** LACTATE, SHUTTLE, LACTIC ACIDOSIS, ACID–BASE BALANCE

The study of lactate metabolism has its roots in the 1700s, and, as in most fields of study, various hypotheses have come and gone through the years. The purpose of this brief review is to present a concise summary of three topics that are at the forefront of today’s research in lactate metabolism: 1) current state-of-the-art viewpoint of the now well-established cell-to-cell lactate shuttle, 2) antagonistic perspectives of the disputed intracellular lactate shuttle, and 3) countervailing opinions on the role of lactate (La^-) in the acidosis that occurs during exercise. The third topic may seem somewhat disparate from the first two, but, similar to the intracellular lactate shuttle, it is hotly debated at the present time and has widespread implications.

CELL-TO-CELL LACTATE SHUTTLE

What is now known as the cell-to-cell lactate shuttle was introduced by Brooks (9) simply as the lactate shuttle. Since

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its introduction in 1984, this hypothesis has been repeatedly supported by studies using a wide variety of experimental approaches. It posits that La^- formation and its subsequent distribution throughout the body is a major mechanism whereby the coordination of intermediary metabolism in different tissues, and cells within those tissues, can be accomplished. The importance of La^- as a carbohydrate fuel source is underscored by the fact that during moderate-intensity exercise, blood La^- flux may exceed glucose flux (71).

Because of its large mass and metabolic capacity, skeletal muscle is probably the major component of the lactate shuttle, not only in terms of La^- production but also in terms of net La^- uptake and use. Figure 1 illustrates the results of an elegant study by Pagliassotti and Donovan (50). In isolated rabbit muscles perfused with a physiological solution containing bovine red blood cells, they (50) measured net La^- balance across the muscles at various levels of perfusate La^- concentration ($[\text{La}^-]$). At rest, both fast glycolytic and slow oxidative muscles released La^- on a net basis, but as the $[\text{La}^-]$ in the perfusate was increased, both muscle types reversed to a net uptake of La^- . Note, however, that the oxidative muscle reversed to net uptake at a lower perfusate concentration (~2.5 mM) as compared with the glycolytic muscle (~4 mM).

In a study from my own laboratory (29), we observed that the highly oxidative dog gastrocnemius–plantaris–superficialis (GP) muscle group *in situ* exhibited net La^- uptake when perfused with an elevated $[\text{La}^-]$ (~9 mM). Additionally, when metabolic rate was increased by stimulating the muscle to contract, the rate of net La^- uptake increased along with the steady-state oxygen uptake.

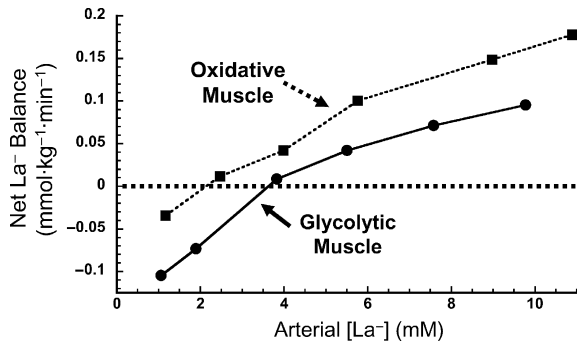


FIGURE 1—Net La^- balance in rabbit muscles of differing fiber types: glycolytic (gracilis, ~99% type IIb fibers) and oxidative (soleus, ~98% type I fibers). Values below the dashed line at 0 indicate net La^- release, whereas values above the line indicate net La^- uptake. Note that the oxidative muscle shifts to net uptake at a lower perfusate $[\text{La}^-]$ (~2.5 mM) as compared with the glycolytic muscle (~4 mM). Redrawn with permission from Pagliassotti and Donovan (50).

Accordingly, when blood $[\text{La}^-]$ increases to the range of 2.5–4.0 mM and greater, both resting and exercising muscles can become sites of net uptake.

In humans, Richter et al. (55) catheterized a femoral artery and vein, measured femoral venous blood flow, and thus evaluated La^- exchange across the quadriceps muscle during different exercise conditions. The quadriceps released La^- during rest and contractions. However, when arm exercise was added to the leg exercise, arterial $[\text{La}^-]$ increased and the quadriceps reversed from net La^- output to net uptake. More recently, van Hall et al. (74) measured net La^- balance across the arms and legs of elite cross-country skiers during 40 min of continuous roller-skiing. During this period of arm plus leg exercise, the arms released La^- , whereas the legs took up La^- ; the net leg La^- uptake was tightly correlated with lactate delivery. Accordingly, studies of exercising humans agree with studies of isolated animal muscle that, depending on the blood $[\text{La}^-]$ and metabolic rate, muscles can be primary sites of La^- uptake. Furthermore, as emphasized by Brooks (10), muscles contracting either *in situ* or *in vivo* typically release La^- transiently after contractions begin, and then they revert to either zero net La^- exchange or even to net La^- uptake as the contractions continue. This pattern has been called the “Stainsby effect” (10), in recognition of the fact that Wendell Stainsby’s lab was one of the first to report this phenomenon (76).

What is the fate of the La^- taken up by muscle? Again employing the canine GP *in situ*, my laboratory (37) followed the metabolic fate of $[\text{U}-^{14}\text{C}]$ lactate both at rest and during contractions, creating a balance sheet. As illustrated in Figure 2, most of the label (~55%) remained in the muscle extract of resting muscle, perhaps in the form of La^- , pyruvate, amino acids, or metabolites in the glycolytic–glyconeogenic and/or triacylglycerol–free fatty acid pathways (13). In resting muscle, the remainder of the ^{14}C label appeared in glycogen, amino acids and pyruvate

released from the muscle, and $^{14}\text{CO}_2$ (representing La^- oxidation) (37). Overall, it seemed that resting muscle could only oxidize La^- slowly because of a low metabolic rate, and that it could act as a passive reservoir. In resting muscle, net conversion of La^- to glycogen is more prevalent in muscles of predominantly glycolytic fiber type (18,50). In contracting muscle, the story is dramatically different. As shown in Figure 2, the vast majority (~83%) of the ^{14}C label from La^- appeared as $^{14}\text{CO}_2$, representing La^- oxidation in the active muscle. Thus, oxidative muscles exercising at moderate intensities in a steady state are avid users of La^- as a fuel.

Recently, these findings have been confirmed and extended in lactate clamp studies in humans. Using a combination of $[3-^{13}\text{C}]$ lactate, $\text{H}^{13}\text{CO}_3^-$, and $[6,6-^2\text{H}_2]$ glucose tracers, Miller et al. (47,48) investigated subjects exercising at a moderate exercise intensity (~55% $\dot{V}\text{O}_{2\text{peak}}$) with La^- infusion to maintain arterialized venous plasma $[\text{La}^-]$ at approximately 4 mM. Overall, they (47) found a significant increase in La^- oxidation accompanied by a decrease in glucose oxidation; the interpretation is that La^- competes successfully with glucose as a carbohydrate fuel source, thus sparing blood glucose for use by other tissues such as the brain. Additionally, Miller et al. (48) found that although La^- to some extent replaced glucose as a gluconeogenic substrate, the absolute rate of gluconeogenesis was unchanged by the lactate clamp. In contrast, in a study by Roef et al. (60), the lactate clamp increased the absolute gluconeogenic rate during low-intensity exercise (~34% $\dot{V}\text{O}_{2\text{peak}}$). Together, these studies demonstrate that La^- was an important gluconeogenic precursor at both low and moderate exercise intensities. These lactate clamp studies, along with many other investigations of different types, emphasize the role of La^- as arguably the most important substrate for gluconeogenesis.

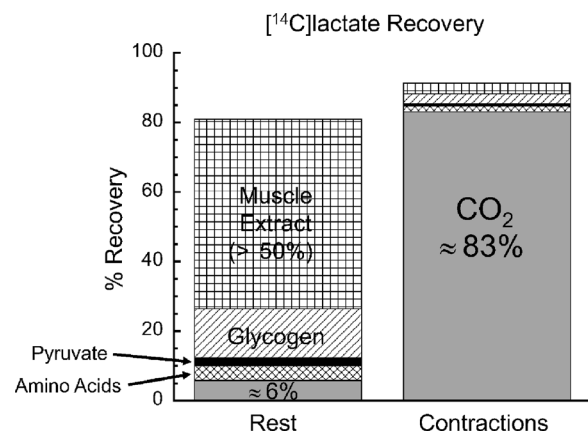


FIGURE 2—Fate of La^- in a perfused canine gastrocnemius muscle as determined from recovery of $[\text{U}-^{14}\text{C}]$ lactate. Note 1) large amount of La^- oxidation in contracting muscle as evidenced by recovery of ^{14}C label in CO_2 , 2) large amount of label in muscle extract of resting muscle, and 3) significant appearance of label in glycogen in resting muscle. Based on data from Kelley et al. (37).

Studies of whole-body La^- balance suggest that removal by the liver accounts for approximately 30% of total removal in resting humans (14). Using arteriovenous measurements across the liver, Nielsen et al. (49) measured a net hepatosplanchnic La^- uptake of $0.4 \text{ mmol}\cdot\text{min}^{-1}$ in resting subjects. During exercise at approximately 75% $\dot{V}\text{O}_{2\text{max}}$, hepatosplanchnic blood flow decreased from about 1.6 to $0.7 \text{ L}\cdot\text{min}^{-1}$, but net La^- uptake more than doubled to $1.0 \text{ mmol}\cdot\text{min}^{-1}$. However, in cases where blood flow diminished more markedly, and hepatosplanchnic venous oxyhemoglobin saturation declined to 6–10%, the arteriovenous La^- difference approached zero, indicating that La^- delivery can become limiting for liver removal of La^- .

Because cardiac muscle is more highly oxidative than even the most oxidative skeletal muscle (34), it is not surprising that the heart is an active La^- consumer. Evidence from several different experimental approaches suggests that as blood $[\text{La}^-]$, myocardial blood flow, and myocardial $\dot{V}\text{O}_2$ increase, La^- becomes the preferred fuel for the heart, accounting for as much as 60% of the substrate used by human myocardium (69,23). Tracer studies indicate that essentially all of the La^- taken up by the heart is oxidized as an aerobic fuel (69).

Even the brain can take up La^- from the blood (17). Figure 3 illustrates the global cerebral arteriovenous $[\text{La}^-]$ difference during rest, progressive incremental exercise, and recovery. As arterial $[\text{La}^-]$ increased progressively from resting values ($\sim 1 \text{ mM}$) to about 12 mM at the end of exercise, and on to about 14 mM early in recovery before declining back towards rest, the arteriovenous difference across the brain showed essentially the same pattern. Although the contribution of brain uptake to whole-body La^- uptake is negligible, it is of great interest in the consideration of brain metabolism *per se* as postulated in the astrocyte–neuron lactate shuttle (51). Recently, Schurr (64) has hypothesized that La^- is the primary product of cerebral glycolysis, whether the brain is at rest or activated, and whether the metabolic conditions are aerobic or anaerobic. As a result, La^- becomes the predominant fuel

for the tricarboxylic acid cycle (via reconversion back to pyruvate), a situation that is very similar to that in skeletal muscle.

With consideration of isotopic tracer studies in addition to other approaches, we arrive at the following scenario. Glycolytic muscle fibers are likely to be producing and releasing La^- during moderate- to high-intensity exercise. Whereas some of this La^- escapes into the circulation, some of it may diffuse to neighboring oxidative muscle fibers, which can remove it from the blood and oxidize it (8,70). La^- released into the blood can be taken up by other skeletal muscle fibers that may be at rest or moderately exercising. Most of the La^- taken up by skeletal muscles is removed through use as an oxidative fuel, with the absolute rate depending on the metabolic rate of both exercising and resting muscles (2,37,45,70). Some of the blood La^- is consumed as a fuel by the heart, and some is likely used for gluconeogenesis by the liver. Clearly, La^- exchange is a dynamic process with simultaneous muscle uptake and release at rest and during exercise (9,36,70).

Since its introduction in the early 1980s, the lactate shuttle (cell to cell) has been called the lactate shuttle “hypothesis.” The concept has been expanded because of growing evidence for astrocyte–neuron, lactate–alanine, peroxisomal, and spermatogenic lactate shuttles, which can be considered subcomponents of the overall cell-to-cell lactate shuttle (see Gladden (26) for references). In this model, La^- is an important intermediary in numerous metabolic processes, a mobile fuel for aerobic metabolism, and perhaps a mediator of redox state among various compartments both within and between cells. The essential aspects of the cell-to-cell lactate shuttle are illustrated in Figure 4. See Gladden’s review (26) for additional details. Given the fact that experimental support for the lactate shuttle is essentially unanimous, it is time to remove the “hypothesis” caveat. The cell-to-cell lactate shuttle is now established as the map for whole-body La^- metabolism.

INTRACELLULAR LACTATE SHUTTLE

Brooks proposed an intracellular lactate shuttle in 1998 (10) and provided supportive data in a 1999 paper (12). A central tenet of this intracellular shuttle was that La^- is an inevitable product of glycolysis, particularly during rapid glycolysis, because lactate dehydrogenase (LDH) has the highest V_{max} of any enzyme in the glycolytic pathway, and the K_{eq} for pyruvate to La^- is far in the direction of La^- and NAD^+ (8,10–12). Given this information, Brooks et al. (11) questioned how it would be possible for La^- to be converted back to pyruvate in the cytosol, thus permitting oxidation of La^- by well-perfused tissues. The Brooks group (11,12,19) has reported evidence of the following key components of an intracellular lactate shuttle in skeletal muscle: 1) direct uptake and oxidation of La^- by isolated mitochondria without prior extramitochondrial conversion of La^- to pyruvate, 2) presence of an intramitochondrial

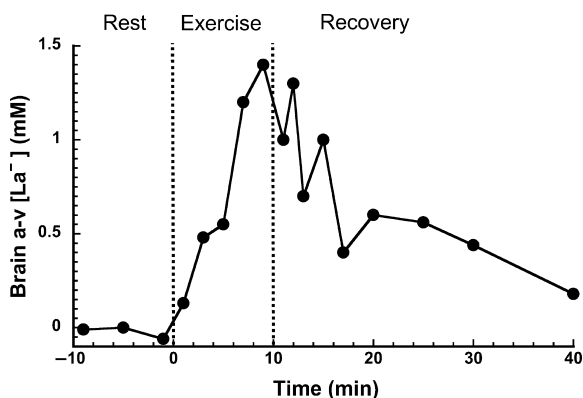


FIGURE 3—Global cerebral arteriovenous $[\text{La}^-]$ difference during rest, progressive incremental exercise, and recovery. Redrawn with permission from Dalsgaard et al. (17).

NADH and, therefore, their uptake from adjacent cytosolic locations. At the same time, sites of cellular glycolysis would create driving concentrations of La^- ; the primary end-product of glycolysis would be La^- from the high activity of LDH, as described earlier. This situation would lead to the highest La^- production and concentration at cytosolic locations remote from mitochondria. Then, because of the relatively higher $[\text{La}^-]$ as compared with [pyruvate], La^- would be the primary species diffusing to areas near mitochondria. The $[\text{La}^-]$ is typically about 10–200 times greater than [pyruvate] in skeletal muscle biopsies (63). Adjacent to mitochondria, La^- and NAD^+ would be converted back to pyruvate and NADH via LDH for uptake into the mitochondria. Such a scheme would accommodate ready La^- production with subsequent oxidation and less transport of La^- out of the cell. This alternative intracellular lactate hypothesis was originally proposed by Stainsby and Brooks (68) in 1990. It is also noteworthy that Yoshida et al. (81) reported that $[\text{La}^-]$ would have to be on the order of 69–139 times greater than pyruvate concentration to achieve similar oxidation rates by isolated mitochondria, a ratio that can occur in skeletal muscle during recovery from intense exercise (63).

The model described above is consistent with the compartmentation of metabolism as described in several studies. James and colleagues (33) have proposed that the Na^+/K^+ -ATPase pump derives its energy heavily from glycolysis that is closely associated with the pump; this idea has recently been supported in studies of mechanically skinned skeletal muscle fibers (20). Several investigators have presented evidence that there is also a functional compartmentation of glycolysis with the sarcoplasmic reticulum (21). Is it possible that La^- derived from glycolysis affiliated with Na^+/K^+ ATPase activity is shunted towards subsarcolemmal mitochondria, whereas La^- derived from glycolysis associated with sarcoplasmic Ca^{2+} pumping is shunted towards intermyofibrillar mitochondria? Perhaps future studies will provide evidence in this regard.

Recent observations of Hashimoto et al. (31) from the Brooks laboratory provide another structural basis for the operation of a nonmatrix intracellular lactate shuttle. Employing the techniques of confocal laser-scanning microscopy, and immunoblotting after immunoprecipitation in L6 skeletal muscle cells, Hashimoto et al. (31) found evidence suggesting that LDH, MCT1, the single-span transmembrane glycoprotein CD147, and cytochrome oxidase are colocalized in the inner mitochondrial membrane, with the LDH enzyme apparently residing on the outer surface of the inner membrane. They (31) have called this a lactate oxidation complex. Hashimoto and Brooks (30) enumerate their experimental evidence supporting the existence of this complex in another paper in this symposium, and they illustrate it in their Figure 1. Whereas such a complex might facilitate the operation of an intracellular lactate shuttle, it need not be a *sine qua non* for the process. Nevertheless, potential location of LDH loosely attached to the outside of

the inner mitochondrial membrane rekindles the possibility that such LDH might be susceptible to loss during the isolation of mitochondria from muscle tissue. Hopefully, future studies will provide conclusive evidence with regard to LDH loss versus contamination in experiments using isolated mitochondria.

LACTIC ACIDOSIS

One of the first physicochemical approaches to acid–base balance in human blood took the form of the Henderson–Hasselbalch equation (1918, as cited by Corey (16)):

$$\text{pH} = \text{pK}' + \log [\text{HCO}_3^-]/(\text{SCO}_2 \times \text{PCO}_2)$$

where pH is the negative logarithm of $[\text{H}^+]$, pK is the negative logarithm of the dissociation constant for carbonic acid to bicarbonate and hydrogen ion, SCO_2 is the solubility coefficient of carbon dioxide (CO_2) in plasma, and PCO_2 is the partial pressure of CO_2 in plasma. In this view of acid–base balance, plasma $[\text{H}^+]$ is regulated/determined by two variables, PCO_2 and $[\text{HCO}_3^-]$. Later in the 20th century, Siggaard-Andersen (65) recognized that the Henderson–Hasselbalch equation alone provides an insufficient description of acid–base balance and established the concept of base excess (16). Base excess is the number of milliequivalents of acid or base needed to titrate 1 L of blood to pH 7.40 at 37°C at a PCO_2 of 40 mm Hg. Subsequently, base excess became the predominant approach to clinical acid–base balance (16,78). As outlined by Corey (16), the base excess approach describes acid–base balance on the basis of two variables, base excess and PCO_2 , and it has several essential features: 1) the quantity of H^+ added to, or removed from, blood or other body fluids is considered to determine the final $[\text{H}^+]$, and 2) plasma membranes may be permeable to H^+ (or HCO_3^-), allowing intracellular as well as extracellular chemical reactions to influence $[\text{H}^+]$.

In the context of H^+ production and consumption, a misconception (27) arose in the field of exercise physiology and, perhaps, other areas of study as well. This fallacy was that lactic acid (HLA) is the species involved in biochemical reactions. In other words, it is HLA that is either produced or consumed biochemically in the LDH reaction. Accordingly, the error was advanced in acid–base balance as follows. Because it is HLA that is produced as the end-product of glycolysis, especially during intense exercise, and HLA is more than 99.5% dissociated at physiological pH values, the rationale was that HLA was produced and then dissociated to release H^+ , reducing pH and causing an intracellular lactic acidosis.

Recently, Robergs et al. (57–59) carefully detailed the reactions of glycolysis, including the role of H^+ in each step, and illustrated that the reaction catalyzed by LDH produces La^- , not HLA; in this conclusion, they are clearly correct. In a revival of ideas posited earlier (32), Robergs et al. (57–59) emphasized the viewpoint that production of

La^- in the LDH reaction consumes H^+ and, from their perspective, actually mitigates intracellular acidosis. Not surprisingly, this ignited quite a debate (4,40,41,44).

At the center of this controversy is the question of cause and effect. What are the independent variables, and what are the dependent variables in acid–base balance? There seems to be no disagreement with the idea that PCO_2 (or, in some cases, total CO_2 content) is one of the independent determinants of $[\text{H}^+]$ (16,38,66). From the viewpoint of Siggaard-Andersen (65,66) (as noted above) and Robergs et al. (57), proton production/addition or consumption/removal is also a controlling factor in determining final $[\text{H}^+]$. Scientists studying transporters at the subcellular level also focus on H^+ (and HCO_3^-) transfer across membranes as a causative agent (5). However, Stewart (72) provides an alternative physicochemical view that has three independent, determining variables: 1) PCO_2 (or total CO_2 content in a closed system), 2) total weak acid concentration ($[A_{\text{tot}}]$), and 3) the strong ion difference ($[\text{SID}]$). PCO_2 has been defined earlier. $[A_{\text{tot}}]$ is the total concentration of weak electrolytes/acids in a given body fluid. $[\text{SID}]$ is the difference between the sum of all the strong base cation concentrations and the sum of all the strong acid anion concentrations (e.g., $[\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] - [\text{Cl}^-] - [\text{La}^-]$). Because of space constraints, the Stewart model will not be presented in detail here; the interested reader is referred to other sources (22,35,44,72).

In the Robergs view of acidosis (57), protons are produced and consumed in various reactions of glycolysis; ATP is formed from nonmitochondrial reactions and is hydrolyzed to provide energy for contractions/exercise; and La^- accumulates via the LDH reaction. In this paradigm, the acidosis results from nonmitochondrial ATP hydrolysis, which produces protons, whereas La^- formation actually limits the acidosis by consuming protons. To Robergs (57), there is no such condition as lactic acidosis. To the contrary, in the Stewart model (72), La^- is a strong ion, and its accumulation reduces the $[\text{SID}]$, which causes alterations in the dissociation equilibria of water and weak acids; the end result is that La^- accumulation is at least partly the cause for acidosis, a portion of which could be called lactic acidosis. Further, Stewart (72) has argued forcefully and repeatedly that $[\text{H}^+]$ is not determined by the amount of H^+ added to or removed from a solution, a sentiment echoed by others (22,35,44). “No matter what the biochemical source of protons, these dependent acid–base variables cannot be considered as independent factors in determining their own concentrations” (44).

The Stewart model has raised numerous fascinating issues, such as whether individual H^+ or OH^- ions actually participate substantively in biochemical reactions or membrane transport processes (44). The Stewart model also argues that $[\text{SID}]$ is the major mechanism by which body fluids can affect each other’s $[\text{H}^+]$ values (22,72). Data showing strong ion concentration changes in exercised muscle, and release and uptake of ions to and from

exercised muscle, have been reported; the resulting changes in $[\text{SID}]$ are argued to be causative in acid–base changes in muscle and blood (35). Additionally, the Stewart model has gained acceptance among clinicians who treat critically ill patients (38,39).

To be complete, it should be noted that Stewart’s analysis was not entirely novel. To a significant extent, Stewart reintroduced, clarified, and computerized the concept of physicochemical analysis of body fluid acid–base status, returning to the thinking of Henderson and Van Slyke and other lesser-known investigators of acid–base balance in the early 20th century (35,43). Moreover, $[\text{SID}]$ is the same as the “buffer base” proposed by Singer and Hastings in 1948 (66,67,78).

In the uproar of debate, sometimes more heat is generated than light. In that context, it should be borne in mind that all of the approaches to acid–base balance arise from the same common foundation and give the same answers in terms of calculated acid–base parameters (15,79). Quoting Wooten (79): “All equilibrium models of acid–base balance use the same basic concept. Under the assumption of equilibrium or a steady-state approximation to equilibrium, some property of the system (e.g., proton number, proton binding sites, or charge, among other possible properties) is enumerated from the distribution of that property over the various species comprising the system, according to the energetics of the system manifested through the relevant equilibrium constants of the various species under a given set of conditions.” So, both the traditional model (proton acceptor sites) and the Stewart model (electrical charge) can be used to calculate the pH in one state versus another (79), and as the measures are taken in two different equilibrium states, the results are independent of the path taken between the two conditions (16,46,79). There is agreement that the Stewart model in particular emphasizes the importance of considering all variables when evaluating acid–base balance; for instance, Stewart’s six equations relating to 1) bicarbonate ion formation equilibrium, 2) carbonate ion formation equilibrium, 3) water dissociation equilibrium, 4) electrical charge balance, 5) weak acid dissociation equilibrium, and 6) conservation of mass (15,72,79). Another method of bookkeeping for $[\text{H}^+]$ is to tally all individual proton releases and uptakes for each reaction in a system on the way from one state to another (46,75); this is the method preferred by Robergs et al. (57).

So, we are still left with the question, what causes a particular $[\text{H}^+]$? The Stewart approach says it is the three independent variables: PCO_2 , $[A_{\text{tot}}]$, and $[\text{SID}]$. Robergs et al. (57) emphasize H^+ production/addition and consumption/removal. Wooten (79,80) contends that 1) Stewart’s case (and, by extrapolation, anyone else’s) for independent variables is “without experimental support”; that 2) without actual mechanistic data, the debate of causality is “more philosophical than physiological”; and that 3) this question cannot be answered on the basis of thermodynamics alone. Nevertheless, Corey (16) summarizes a few examples of

evidence that might support the Stewart model's assertion that changes in SID cause shifts in the position of water equilibrium to cause changes in $[H^+]$. As one example, ionic charge may disrupt hydrogen bonds and affect the properties of water. Additional studies are required in this regard as well as studies at the molecular level where proton and bicarbonate transporters are being examined in minute detail (56). Whereas the emphasis has been on the protons and bicarbonate, closer examination reveals that strong ions are involved either as symported or antiported species (56). Hopefully, further study will reveal which ions are actually being regulated and are, therefore, causative in nature.

Approximately 80–100% of lactate transfer across the sarcolemma occurs via either diffusion of undissociated HLa or facilitated transport with MCT (24,52,61). In both cases, a proton is transferred with (or appears with) La^- . What is the significance of this process from exercising muscle to plasma? From the Stewart perspective, a strong ion (La^-) has been added to the plasma, which would cause an increase in $[H^+]$. From the Robergs/traditional acid–base perspective, a proton has been added to the plasma, which would cause an increase in $[H^+]$. Therefore, both viewpoints suggest a lactic acidosis in plasma.

Given 1) the central role of La^- in the difference between the rest and exercise states of both muscle and blood, 2) the possibility that La^- may play a causative role as a strong ion, 3) the overall uncertainty about cause and effect in acid–base balance, and 4) compatibility between different models regarding the effect of HLa/ La^- on plasma acid–base balance, there is no compelling reason at this time to change the terminology from “lactic acidosis” to “non-mitochondrial ATP hydrolytic acidosis.”

CONCLUSIONS

In conclusion, this brief review has summarized the current status of three topics in the study of La^- metabolism: 1) the

cell-to-cell lactate shuttle, 2) the intracellular lactate shuttle, and 3) the role of La^- in the acidosis of exercise. With regard to the cell-to-cell lactate shuttle, the verdict is in: La^- is a central player in cellular, regional, and whole-body metabolism. Far from being a dead-end metabolite, La^- stands at the crossroads of metabolism. The cell-to-cell lactate shuttle has been repeatedly supported by numerous experimental studies, and it now provides the context for interpretation of overall, whole-body lactate metabolism.

In contrast, the intracellular lactate shuttle is being strongly debated. It seems likely that La^- is the primary product of glycolysis, particularly in intracellular compartments that are distant from mitochondria. Much of this La^- probably diffuses to areas adjacent to mitochondria, perhaps into the intermembrane space near a lactate oxidation complex located within the inner mitochondrial membrane. Conversion of La^- back to pyruvate most likely occurs outside the inner mitochondrial membrane rather than in the mitochondrial matrix. Future studies will clearly establish the intracellular role of La^- in skeletal muscle oxidative metabolism.

Another controversial area in La^- metabolism is the role of La^- in the acidosis of exercise. For much of the past century, lactic acid production and its subsequent dissociation have been considered a major factor in the acidosis of intense exercise. Recently, a careful evaluation of the reactions of the glycolytic pathway has reintroduced the concept that La^- , not lactic acid, is the product of the LDH reaction, and that, accordingly, La^- formation actually attenuates acidosis. This view is at odds with the notion that La^- is a major contributor to the [SID], which is considered an independent determinant of $[H^+]$ by some. A review of the literature reveals that all of the various approaches to acid–base balance arise from the same common foundation and give the same answers in terms of calculated acid–base parameters. Somewhat surprisingly, there is no consensus on the actual causes/mechanisms of $[H^+]$. Nevertheless, at this time, there is insufficient evidence to eliminate the term “lactic acidosis.”

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