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Lactate, A Phoenix Rising in Contemporary Biology
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Abstract

After a Century it’s time to turn the page on understanding of lactate metabolism and appreciate that lactate shuttling as an important component of intermediary metabolism in vivo. Cell-Cell and intracellular Lactate Shuttles fulfill purposes of energy substrate production and distribution as well as cell signaling under fully aerobic conditions. Recognition of lactate shuttling came first in studies of physical exercise where roles of driver and recipient cells and tissues were obvious. Moreover, the presence of lactate shuttling as part of postprandial glucose disposal has been recognized. Mitochondrial respiration creates the physiological sink for lactate disposal in vivo. Repeated lactate exposure from regular exercise results in adaptive processes such as mitochondrial biogenesis and other healthful circulatory and neurological characteristic such as improved physical work capacity, metabolic flexibility and cognition. The importance of lactate and lactate shuttling in healthful living is further emphasized when lactate signaling and shuttling are dysregulated as occur in illness and injury. Like a Phoenix, lactate rises again in importance in 21st Century Biology.
Introduction

The story of lactate and its role in physiology and medicine may be a century old, but has change dramatically in the last three decades \(^1\text{-}^4\). No longer conceived of as a dead-end metabolite, a fatigue agent and metabolic poison, in contemporary physiology lactate is seen as a major metabolic intermediate that has wide ranging impacts as an energy substrate utilization, cell signaling and adaptation \(^2\text{-}^5\). Now, the presence of lactate shuttling is recognized in diverse fields such as wound healing \(^6\), cancer biology \(^7\), insulin secretion \(^8\), management of sepsis \(^9\), learning and memory \(^10,11\), and treatment of Traumatic Brain Injury (TBI) \(^12\). Hence, in contemporary biology the role of lactate in metabolism needs to be viewed as a Phoenix Rising.

Contributions From Muscle and Exercise Physiology (Cell-Cell and Intracellular Lactate Shuttles)

The Cell-Cell Lactate Shuttle: Origin of the revolution in lactate metabolism is traceable to results on dog muscles made to contract in situ \(^13\). At rest those highly red richly perfused and oxygenated muscles always released lactate. Then, at the onset of contractions lactate release increased, but then switched to net uptake as contractions continued and oxygen consumption rose. Subsequently, use of NADH fluoroscopy \(^14\) and myoglobin cryomicroscopy \(^15\) verified that working muscles were not oxygen limited and that “aerobic glycolysis” was present in resting and working muscles.

Advent of radiotracers and their use in physiology soon showed continuous lactate production under fully aerobic conditions in dogs \(^16\) and rats \(^17,18\) with disposal during exercise by oxidation and conversion to glucose \(^19\). Moreover, in studies on rats recovering from exercise, during the so called “Oxygen Debt” period, showed oxidative disposal (4/5) over gluconeogenesis and glyconeogenesis (1/5) \(^20\text{-}^22\).

Advent of stable, nonradioactive tracers and their use in physiology and metabolism soon replicated in humans what was shown in mammalian models \(^23\text{-}^25\). Subsequently, combined use of arterial venous differences (a-v) and blood flow as well as isotopic tracers showed simultaneous lactate production and oxidative disposal (turnover) within resting and working human skeletal muscles \(^25,26\). The same technologies have been employed to show lactate turnover in human heart \(^27\text{-}^29\) and brain \(^30\).
Complimentary to determinations of lactate disposal via oxidation were those determining lactate disposal via gluconeogenesis. Hence it is fair to state that while a minority of lactate disposal is accomplished via gluconeogenesis under postabsorptive conditions, lactate is the most important gluconeogenic precursor\textsuperscript{31-33}

In sum, the above-cited work shows continuous aerobic (not oxygen-limited) lactate turnover in humans and mammalian model systems. Further, the work shows two of three features of the Lactate Shuttle that are lactate production in driver cells and disposal in recipient cells; signaling being a third feature of the Lactate Shuttle\textsuperscript{1,4,34}.

The Intracellular Lactate Shuttle: The above-cited studies show simultaneous lactate uptake, production and oxidation in vivo\textsuperscript{25,26}. However, those studies did not provide information on the intracellular path of lactate oxidation. Hence, studies on isolated mitochondria\textsuperscript{35-42} and muscles\textsuperscript{43} were called for.

The cellular respiratory apparatus is comprised a mitochondrial reticulum\textsuperscript{44-46} that extends from the sub-sarcolemmal domain to deep within fibers. To oxidize energy products of glycolysis the reticulum contains both lactate (mMCT)\textsuperscript{35} and pyruvate (mPC) transporters\textsuperscript{47,48}. Importantly, because the product of glycolysis is lactate, not pyruvate\textsuperscript{49}, mitochondrial uptake and oxidation far exceeds that of pyruvate. Hence, studies of muscle lactate oxidation and muscle mitochondria led to discovery of the Mitochondrial Lactate Oxidation Complex (mLOC)\textit{in vivo}.

The mLOC contains several essential components of lactate oxidation: an MCT, its membrane chaperone Basigin (BSG or CD147), LDH and cytochrome oxidase (COx) as seen in muscle\textsuperscript{41}, liver\textsuperscript{40,50}, and brain\textsuperscript{42}, and various model systems such as brain slices\textsuperscript{51}, primary neuronal cultures\textsuperscript{38,42}, normal breast and transformed breast cancer cells\textsuperscript{52}, and tumors\textsuperscript{53}. Confirmation of a preference of mitochondrial lactate over pyruvate oxidation comes from studies of hyperpolarized lactate in muscles\textit{in situ}\textsuperscript{43}.

In sum, intracellular lactate disposal is accomplished by a transport mechanism for direct mitochondrial uptake and oxidation that involves a mLOC which likely works in parallel with malate-aspartate, glycerol-phosphate, pyruvate and other shuttles to manage the lactate load from glycolysis under normal and stressful conditions.
Contributions From Studies of Postprandial Metabolism (The Glucose Paradox and Lactate Shuttling)

Studies of postprandial glucose metabolism show what has been termed as the “Glucose Paradox,” or “Indirect Pathway of Hepatic Glycogen Synthesis”\(^{54}\). This concept asserts that dietary glucose released into the hepatic portal vein bypasses the liver and goes to the periphery where glycolysis converts glucose to lactate that is subsequently released into the systemic circulation and taken up by liver from the arterial circulation for glycogen synthesis. This, paradoxical, “Indirect” pathway of hepatic glycogen synthesis is to be contrasted with the “Direct” pathway in which dietary glucose from the gut is taken up and converted to liver glycogen on first circulatory pass.

The initial concept, developed on the basis of studies on lab animals, has been replicated on healthy, postprandial humans. Gerich and colleagues confirmed that glycolysis is the main initial postprandial fate of glucose, accounted for \(\approx 66\%\) of overall disposal while oxidation and storage accounted for \(\approx 45\%\). However, the majority of hepatic glycogen synthesis in postprandial humans (\(\approx 73\%\)) was formed via the Direct Pathway\(^{55}\).

In sum, like the event of physical exercise in which lactate plays a prominent role in energy substrate production and disposal, lactate also plays an important role in carbohydrate disposal after eating\(^{56}\).

Lactate Shuttling and Metabolic Signaling: Redox, ROS, Allosteric Binding and Histone Lactylation

The effects of increases in cell work and lactate production on Redox, ROS, Allosteric Binding and Histone Lactylation have been recently reviewed\(^5\). Briefly, cell work leads to lactate production and changes in the cellular Lactate/Pyruvate\(^{57}\) ratio that accompanies changes in the cellular \(\text{NAD}^+ / \text{NADH}\) ratio and subsequent metabolic and regulatory effects in driver and recipient cells.

**Cell Redox:** Aside from the major effects of muscle contraction and glycolysis on the \(\text{NAD}^+ / \text{NADH}\) ratio, lactate production and removal can change the ratio of reduced to oxidized glutathione (GSH/GSSG)\(^{58,59}\).
ROS: Lactate can effect cellular production of Reactive Oxygen Species (ROS) via mitochondrial respiration and non-enzymatically via lactate-iron interactions that are capable of generating ROS. Another way in which lactate can effect ROS production is via mitochondrial L-lactate metabolism that generates ROS, specifically hydrogen peroxide ($H_2O_2$). The latter mechanism involves generation of $H_2O_2$ via a flavine-dependent Lactate Oxidase located in the mitochondrial intermembrane space.

Sirtuins: Sirtuins are deacetylases regulated by the equilibrium between nicotinamide (NAM) and NAD$^+$. Sirtuin activation is accomplished via changes in cell redox (i.e., the NAD$^+$/NADH) through the concentration of NAM and the activity of enzyme NAM phosphoribosyl transferase (Nampt). Many investigators are concerned with how the subtle changes in cell redox affect cell homeostasis as occur in apoptosis, inflammation, and other processes. However, more obvious are changes in cell redox with increments in cell work as occur in exercise. At present data are lacking on the change in Nampt activity in working muscle or non-working recipient tissues in which changes in NAD$^+$ and NADH concentrations likely effect sirtuin regulation in vivo.

Cellular Lactate Receptors and Signals: The mechanism by which lactatemia suppresses circulating free fatty acids (FFA) is now known to be due to suppression of adipose lipolysis. Independent of pH, lactate inhibits lipolysis in fat cells through activation of a G-protein coupled receptor (GPR81), now termed hydroxycarboxylic acid receptor 1 (HCAR-1). In studies of mouse, rat and human adipocytes, HCAR-1 appears to act as a lactate sensor with the inhibitory effect on lipolysis operating through cyclic-AMP (cAMP) and cAMP response element binding (CREB).

Recently, our knowledge of the role of lactate signaling was expanded via discovery that Transforming Growth Factor Beta 2 (TGF-β2) is secreted from adipose. Because TGF-β2 improved glucose tolerance in mice, the authors concluded that exercise training improves metabolic regulation through an inter-organ (adipose to liver) communication via a “lactate-TGF-β2 signaling cycle.”

Lactylation of Histones: Regulation of gene expression by lactylation of 28 lysine residues on histones has been demonstrated. The addition of lactate in addition to phosphate, methyl and acetyl tags to histones is yet another, epigenetic, way by which the genome and intermediary metabolism are regulated. As noted above, lactate release from driver cells into the circulation...
as occurs in physical exercise and other stressful conditions has the potential to affect gene regulation in diverse cells around the body during and after physical exercise.

The purported effects of lactate signaling HCAR-1, TGF-β2, Nampt and lactylation of histones observed in rodent and cell models await validation in humans. However, for the present it is certain that lactate both inhibits lipolysis and mitochondrial FFA oxidation and stimulates mitochondrial biogenesis and glucose tolerance and lipid oxidation in humans in vivo. Therefore, the new results are encouraging as the signaling patterns are consistent with what is known about the roles of lactate in physiology and metabolism.

**Lactate Shuttling: Alternating Roles of Driver and Recipient Cells**

Lactate flux between cells and tissue beds depends on concentration and pH differences. Monocarboxylate transporters (MCTs) are bidirectional symporters sensitive to trans-stimulation by lactate and hydrogen ion gradients. Not surprisingly driver and recipient cells can switch roles depending on conditions. For instance, when exercise starts, muscles release lactate, but switch to consumption as oxygen consumption rises. Conversely, postprandial glucose uptake and lactate production by muscles provide substrate to the body corpus as in the Glucose Paradox. Via lactate shuttling working muscle can fuel the beating heart and learning brain as well provide gluconeogenic substrates to the splanchnic organs.

**Phasic Lactate Shuttling: Lessons from the Heart**

Tracer studies allow us to know that the heart produces lactate even as it acts as a lactate sink displaying net uptake from the arterial circulation. Because systole interrupts coronary blood flow, especially in the endocardium, then the presence of a phasic intra-cardiocyte lactate shuttle is indicated. At a resting heart rate of 60 bpm, there occurs 200 ms of systole that is powered by glycolysis followed by 800 ms of diastole for oxidative recovery and lactate clearance. In the future, hyperpolarized MRS or other technology will allow for detection of lactate production, net uptake and oxidative disposal within a cardiac cycle.

**Summary**

It’s time to turn the page on understanding of lactate metabolism and consider lactate shuttling as an important component of intermediary metabolism in vivo. The presence of Cell-Cell and intracellular Lactate Shuttles fulfill purposes involving energy substrate production and sharing
as well as cell signaling under fully aerobic conditions. Recognition of lactate shuttling came first in studies of physical exercise where roles of driver and recipient cells and tissues were obvious. However, independently the presence of lactate shuttling as part of postprandial glucose disposal was recognized \(^{54,55}\). Mitochondrial respiration creates the physiological sink for lactate disposal \textit{in vivo}. Repeated lactate exposure from regular exercise results in adaptive processes such as mitochondrial biogenesis and other healthful circulatory and neurological characteristics such as improved physical work capacity, metabolic flexibility \(^1\) and cognition \(^{10,11}\). The importance of lactate and lactate shuttling in healthful living is further emphasized when lactate signaling and shuttling are dysregulated as occur in illness \(^{72}\) and injury \(^{73,74}\). Like a Phoenix, lactate rises again in importance in 21\textsuperscript{st} Century Biology.

References


