Cell Metabolism
Review

The Science and Translation of Lactate Shuttle Theory

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Once thought to be a waste product of anaerobic metabolism, lactate is now known to form continuously under aerobic conditions. Shuttling between producer and consumer cells fulfills at least three purposes for lactate: (1) a major energy source, (2) the major gluconeogenic precursor, and (3) a signaling molecule. "Lactate shuttle" (LS) concepts describe the roles of lactate in delivery of oxidative and gluconeogenic substrates as well as in cell signaling. In medicine, it has long been recognized that the elevation of blood lactate correlates with illness or injury severity. However, with lactate shuttle theory in mind, some clinicians are now appreciating lactatemia as a "strain" and not a "stress" biomarker. In fact, clinical studies are utilizing lactate to treat pro-inflammatory conditions and to deliver optimal fuel for working muscles in sports medicine. The above, as well as historic and recent studies of lactate metabolism and shuttling, are discussed in the following review.

Introduction

Once thought to be the consequence of oxygen deficits in contracting skeletal muscle, we now know that the L-enantiomer of the lactate anion is formed and utilized continuously in diverse cells under fully aerobic conditions. In fact, as the product of one metabolic pathway (glycolysis) and the substrate for a downstream pathway (mitochondrial respiration), lactate can be regarded as the link between glycolytic and aerobic pathways (Figure 1). Importantly, according to the lactate shuttle hypothesis, this linkage occurs under fully aerobic conditions and can transcend compartment barriers and occur within and among cells, tissues, and organs (Brooks, 1984, 2002, 2009). In contrast to its early portrayal as a metabolic waste product and fatigue agent, lactate is the chief messenger in a complex feedback loop. Short-term challenges to adenosine triphosphate (ATP) supply stimulate lactate production, leading to immediate, short- and long-term cellular adaptions to support ATP homeostasis. The physiology and biochemistry of this topic were extensively reviewed by Bruce Gladden in 2004 and should be consulted (Gladden, 2004), but subsequently new information has become available, particularly with regard to the role of lactate and lactate shuttle, to understand basic physiology and metabolism as well as to treat injuries and illnesses.

At the whole-body level, lactate metabolism is understood to be important for at least three reasons: (1) lactate is a major energy source (Bergman et al., 1999b; Brooks et al., 1991a; Mazzeo et al., 1986; Stanley et al., 1985, 1986); (2) lactate is the major gluconeogenic precursor (Bergman et al., 2000; Emhoff et al., 2013b; Meyer et al., 2002a; Stanley et al., 1988); and (3) lactate is a signaling molecule with autocrine-, paracrine- and endocrine-like effects and has been called a "lactormone" (Brooks, 2002, 2009; Hashimoto et al., 2007). "Cell-cell lactate shuttle" and "intracellular lactate shuttle" concepts describe the roles of lactate in delivery of oxidative and gluconeogenic substrates as well as in cell signaling (Brooks, 2002, 2009) (Figure 2). Examples of the cell-cell lactate shuttles include lactate exchanges between white-glycolytic and red-oxidative fibers within a working muscle bed and between working skeletal muscle and heart (Bergman et al., 2009; Gertz et al., 1981, 1988), brain (Glenn et al., 2015b; Quistorff et al., 2008; van Hall et al., 2009), liver and kidneys (Bergman et al., 2000; Emhoff et al., 2013b; Meyer et al., 2002b; Woerle et al., 2003), astrocytes and neurons (Pellerin et al., 1998), and vice versa (i.e., neurons and astrocytes) (Liu et al., 2017) (Figure 1B). Examples of intracellular lactate shuttles include cytosol-mitochondrial (Brooks et al., 1999a; Butz et al., 2004) and cytosol-peroxisome exchanges (McClelland et al., 2003). Indeed, most if not all cell-cell and intracellular lactate shuttles are driven by a concentration or pH gradient or by redox state.

Subsequent to and coincident with findings of high rates of lactate flux, oxidation, and gluconeogenesis in healthy rodents (Brooks and Donovan, 1983; Donovan and Brooks, 1983) and humans during rest and submaximal exercise (Mazzeo et al., 1986; Stanley et al., 1988) were observations that lactate traverses membrane barriers by facilitated, carrier-mediated lactate anion and proton exchange (Dubouchaud et al., 2000; Garcia et al., 1994; Roth and Brooks, 1990a, 1990b) involving a family of lactate/pyruvate monocarboxylate transport (MCT) proteins (Garcia et al., 1994, 1995; Price et al., 1998). MCT protein isoform expression patterns vary with muscle fiber type (Hashimoto et al., 2005, 2006), and MCTs are expressed in tissues and cellular organelles that rapidly exchange lactate, including the brain (Hashimoto et al., 2008; McClelland et al., 2003; Pellerin et al., 2005). Importantly, MCTs are bidirectional (Brown and Brooks, 1994), allowing for tissues to switch between lactate release and uptake depending on changes in concentration and pH. For example, lactate release from a muscle occurs when contractions start and rate of lactate appearance (Ra) increases; this is followed by lactate uptake as muscle oxygen consumption reaches a new steady state and the rate of lactate disappearance (disposal, Rd) exceeds production and hence Ra of lactate (Bergman et al., 2009;

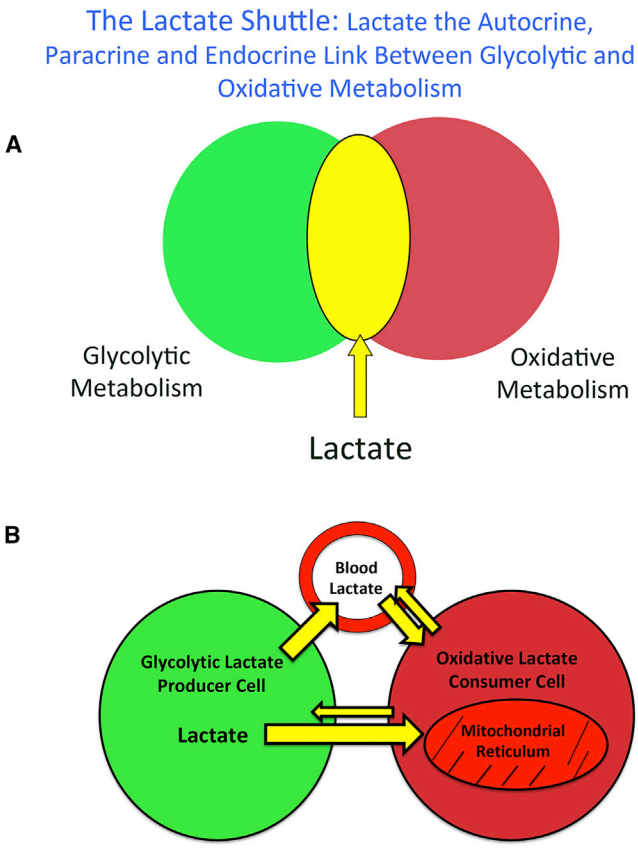

Figure 1. The Lactate Shuttle Concept

(A) The lactate shuttle concept depicting lactate as the vehicle linking glycolytic and oxidative metabolism. Linkages between lactate "producer" and "consumer" exist within and among cells, tissues, and organs. As the product of one metabolic pathway (glycolysis) and the substrate for a downstream pathway of disposal (mitochondrial respiration), lactate is the link between glycolytic and aerobic pathways. Importantly, according to the lactate shuttle hypothesis, this linkage occurs continuously under fully aerobic conditions, can transcend compartment barriers, and can occur within and among cells, tissues, and organs. Modified from Brooks, 1984.

(B) Depiction of the cell-cell lactate shuttle within a tissue bed. Lactate exchanges between blood and producer and consumer cells moving down lactate and proton concentration gradients. Although both cell types are glycolytic, lactate concentration is greatest in highly glycolytic producer cells and lowest in highly oxidative consumer cells in which lactate is an oxidizable substrate in the mitochondrial reticulum. Depending on the physiological circumstance, such as continuous physical exercise, blood lactate concentration will be intermediate: that is, higher than in consumer cells but lower than in producer cells. Hence, lactate flux from blood to oxidative consumer cells within working muscle sometimes achieves net muscle uptake even while lactate is produced in highly glycolytic cells (Bergman et al., 1999b). Cell-cell lactate shuttling is typical of continuous exercise and diverse other situations such as astrocyte-neuron lactate shuttle (Pellerin and Magistretti, 2012). Modified from Brooks, 1984.

Stanley et al., 1986). Further, changes in MCT expression can occur rapidly, as happens following neurotrauma in rats (Prins and Giza, 2006).

The roles of lactate as a metabolic substrate and critical signaling molecule continue to gain support with ongoing research (Elustondo et al., 2013; Jacobs et al., 2013). In intact functioning humans (Miller et al., 2002a, 2002b), in working human skeletal muscles (Bergman et al., 1999b; Stanley et al., 1986), as well as in the hearts of those individuals (Bergman et al., 2009; Gertz et al., 1981, 1988), lactate is preferred over glucose as a fuel. Similarly, lactate is preferred over glucose as a fuel in brain preparations (Schurr, 2006, 2008; Schurr and Payne, 2007) and *in vivo* (Hashimoto et al., 2018; van Hall et al., 2009). The astrocyte-neuron lactate shuttle (ANLS) posits that lactate is extruded by astrocytes and then actively consumed and oxidized by neurons involved in glutamatergic signaling (Pellerin et al., 1998). Relevant to lactate shuttling in brain (Barros, 2013; Bélanger et al., 2011), neurons possess the cellular components necessary for glucose uptake and use by an intracellular lactate shuttle (Hashimoto et al., 2008), and a post-trauma neuroprotective role of lactate has been proposed (Holloway et al., 2007; Schurr and Gozal, 2012). From the earliest work on plasma membrane lactate exchange, it was recognized that lactate transporters are symporters moving solute down anion and proton concentration gradients (Roth and Brooks, 1990a, 1990b), which is consistent with more recent studies, for example between astrocytes and neurons (Mächler et al., 2016). Hence, it is not surprising that Bellen and colleagues (Liu et al., 2017) have described a neuron-glia lactate shuttle linked to lipid transfer that may be disrupted in Alzheimer's disease (Bailey et al., 2015).

At both systemic and cerebral levels, it is clear that glucose-lactate interactions are essential in normal physiology as well as pathophysiology. Conditions in which lactate metabolism is important in normal physiological function include: energy supply (Brooks, 1986; Mazzeo et al., 1986; Stanley et al., 1985), maintenance of glycemia (Bergman et al., 2000; Emhoff et al., 2013b; Stanley et al., 1988), maintenance of cerebral metabolism in the face of hypoglycemia (Herzog et al., 2013), cerebral metabolism and signaling (Liu et al., 2017; Pellerin and Magistretti, 1994), and cerebral executive function (Hashimoto et al., 2018). Clinical conditions in which lactate therapy may be efficacious include glucose control (Bouzat et al., 2014; Wolahan et al., 2017), traumatic brain injury (Brooks and Martin, 2015), heart failure (Nalos et al., 2014), dengue (Somasetia et al., 2014), endotoxic shock (Duburcq et al., 2014; Junarsa et al., 2015), inflammation (de-Madaria et al., 2017), immunosuppressive role in sepsis (Nolt et al., 2018), and fluid resuscitation (Marques et al., 2017). Of the several goals in authoring this review, certainly one is to lift the veil of confusion around "lactate": is it a metabolic poison and fatigue agent (Hill, 1924; Hill and Lupton, 1923; Meyerhof, 1920), or are there necessary and positive attributes to lactate formation and disposal (Brooks, 1984; Cori and Cori, 1946)? Most likely, the latter is true.

Physiology

Glycolysis

Since 3000 BCE, beer and wine making were known in ancient Egypt. Historically, it is also known that fermentation makes milk and cabbage sour. Glycolysis in tissues deprived of oxygen results in lactate and acid production and accumulation (Fletcher, 1907; Meyerhof, 1920; Pasteur, 1863). But does glycolysis produce lactate or lactic acid with a 1:1 proton-to-lactate anion stoichiometry in perfused and oxygenated muscles and other tissues of humans and mammalian model systems? Most likely, a 1:1 lactate anion:proton production ratio does not occur in mammalian systems *in vivo*.

Since the inception of modern physiology and biochemistry, researchers have associated lactic acid accumulation with

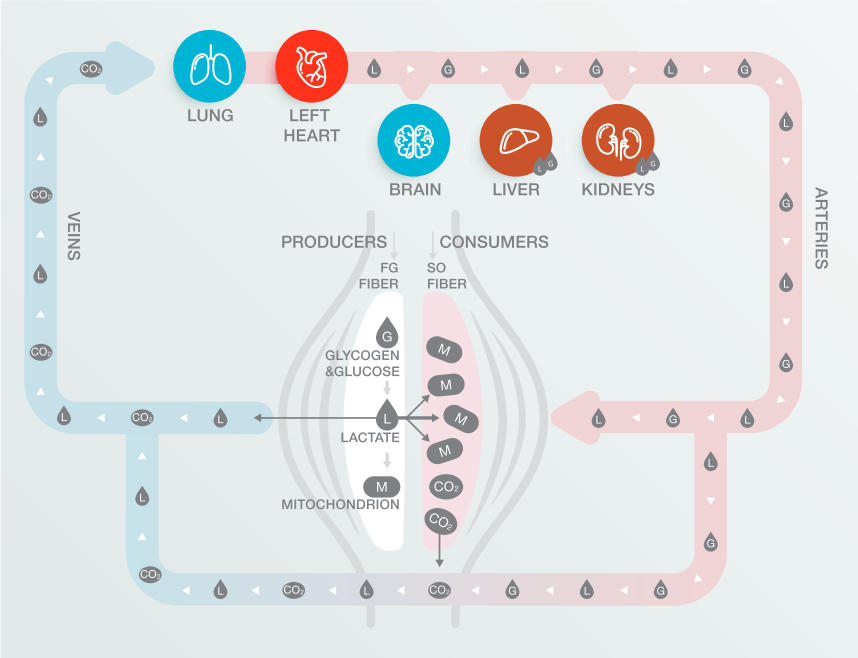

Figure 2. Depiction of the Lactate Shuttle as It Fulfills Three Physiological Functions

Lactate is a major energy source; is the major gluconeogenic precursor; is a signaling molecule with autocrine-, paracrine- and endocrine-like effects; and has been called a "lactormone." "Cell-cell" and "intracellular lactate shuttle" concepts describe the roles of lactate in delivery of oxidative and gluconeogenic substrates as well as in cell signaling. Examples of the cell-cell lactate shuttles include lactate exchanges between white-glycolytic and red-oxidative fibers within a working muscle bed and between working skeletal muscle and heart, brain, liver, and kidneys. Examples of intracellular lactate shuttles include cytosol-mitochondrial and cytosol-peroxisome exchanges. Indeed, most if not all lactate shuttles are driven by a concentration or pH gradient or by redox state. G, glucose and glycogen; L, lactate. Compiled from diverse sources (Brooks, 1984, 2002, 2009).

muscle fatigue (Fletcher, 1907; Hill, 1914; Hill and Lupton, 1923). A then-contemporaneous interpretation of results on electrically stimulated but unperfused and non-oxygenated frog muscle and frog hemi-corpus preparations was that lactic acid accumulation caused muscle fatigue (*vide infra*). Exploring the cause of fatigue was not an experimental purpose of Otto Meyerhof (Meyerhof, 1920); rather, his purpose was to quantitate glycogen-lactate relationships and establish that glycogen was the precursor to lactate. Hence, from its inception there has been confusion about lactic acid production and muscle fatigue.

Additional confusion in discriminating between effects of lactate and lactic acid relates to common occurrences in physiology and metabolism. *In vivo* lactatemia is typically, but not always, accompanied by hydrogen ion accumulation (acidosis) because metabolic stress gives rise to glycolysis, ATP hydrolysis, and carbonic acid formation and dissociation. Then again, because MCTs are symporters moving lactate anions and protons simultaneously, in effect, MCTs are lactic acid transporters. In other situations, when sodium-lactate solutions are given orally or intravenously for experimental or therapeutic purposes, a mild alkalosis results (Miller et al., 2005) Hence, in different situations it is important to consider the individual or combined effects of lactate anions and hydrogen ion.

Lactate and Acidosis

While it remains uncertain whether glycolysis produces lactate or lactic acid, it is certain that acidosis occurs in exercise and other conditions. However, the parameter we describe as pH in physiology and pathophysiology is far more complicated than the production of protons in any single metabolic pathway. From the work of Peter Stewart, we realize that blood pH ($[H^+]$) is a dependent variable influenced by the partial pressure of CO_2 (PCO_2), the concentration of weak acid buffers ($[A_{tot}]$, in plasma mainly amino acids and proteins), and the strong ion difference (SID), which is calculated as the sum of the strong cation concentrations minus the sum of the strong anions (Kowalchuk et al., 1988; Miller et al., 2005):

$$SID\ (meq/L) = ([Na^+] + [K^+] + [Ca^{++}] + [Mg^{++}]) - ([Cl^-] + [Lac^-]).$$

Although technical difficulties and conceptual criticisms of the Stewart SID approach have precluded its universal adoption in clinical situations (Morgan, 2009), in theory and for research purposes the Stewart approach does inform that lactate anion (Lac^-) is but one factor increasing $[H^+]$ (decreasing pH) and that whether glycolysis produces protons or not, protons from glycolysis do not affect blood $[H^+]$ on a one-to-one basis. Further, the Stewart approach helps us understand why infusion of lactate-containing solutions (e.g., Na^+-lactate) raises blood pH. Regardless of tight or loose coupling between rates of lactate and proton production, clearly glycolysis makes lactate; as discussed in this review, this product of glycolysis is an important fuel and signaling molecule. So it is critical to consider the physiological factors that stimulate lactate production. As discussed below, oxygen availability was classically considered to be a primary driver of lactate production, although there are numerous reasons to reconsider this simplistic view.

Lactate and Oxygen Lack (Anaerobiosis)

Discounting for now the Warburg effect in cancer (Warburg et al., 1927; *vide infra*), we now have a good understanding of the disposal of glycolytic flux products during rest and during stressful conditions such as exercise, high altitude exposure, trauma, and sepsis (Figure 3). Importantly, there is no solid experimental support for the traditional view that glycolytic flux is directed to mitochondrial respiration solely through pyruvate uptake by the mitochondrial reticulum. In the past it was assumed by many that the rising lactate abundance in the body indicated anaerobic conditions at the cellular level, but our understanding of lactate as a metabolically valuable carbohydrate has now replaced this traditional view. Experimental support is lacking for the

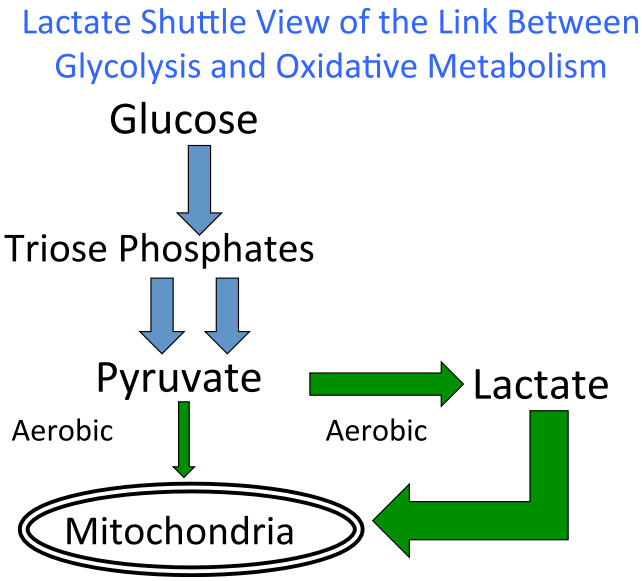

Figure 3. Glycolysis Produces Lactate, Not Pyruvate

There is strong evidence that glucose and glycogen catabolism proceed to lactate production under fully aerobic conditions in studies on intact animals, animal tissue preparations, and humans. Results of studies on human subjects clearly show that lactate production occurs under fully aerobic conditions. In muscles and arterial blood of resting healthy humans, lactate concentration approximates 1.0 mM, while pyruvate concentration approximates 0.1 mM, the lactate/pyruvate (L/P) being 10; the results show that glycolysis progresses to lactate under fully aerobic conditions. Further, in resting muscles of healthy individuals, the intramuscular partial pressure of oxygen (PO_2) approximates 40 Torr, well above the critical mitochondrial PO_2 for maximal mitochondrial respiration (1–2 Torr). Clearly, net lactate production and release occur when oxygen is ample (Bendahan et al., 2017; Connett et al., 1990; Rumsey et al., 1990). During exercise at about 65% of maximal oxygen consumption (VO_2max), lactate production and net lactate release from working muscle beds rise, and the L/P rises more than an order of magnitude (to ~500), but the intramuscular PO_2 remains at 3–4 Torr, well above the critical mitochondrial O_2 level. Hence, it is appropriate to conclude that in healthy humans, glycolysis proceeds to lactate under fully aerobic conditions. Importantly, most (75%–80%) of lactate is disposed of immediately within the tissue or subsequent to release and reuptake by working muscle, with significant uptake and oxidation by heart for oxidation and liver for gluconeogenesis. From diverse sources (Bergman et al., 1999b; Connett et al., 1990; Henderson et al., 2007; Richardson et al., 1998; Stanley et al., 1986).

notion that glycolytic flux is directed to lactate production only when oxygen is lacking. Similarly, there is no evidence that the first step in lactate oxidation (i.e., conversion to pyruvate) occurs in the cytosol of any tissue, including the beating heart or working skeletal muscle, that has a lactate-to-pyruvate concentration ratio (L/P) > 100 (Henderson et al., 2007) and that are net glucose consumers (Bergman et al., 2009). In contrast, there is strong evidence that glucose and glycogen catabolism proceed to lactate production under fully aerobic conditions (Bendahan et al., 2017; Richardson et al., 1998; Rogatzki et al., 2015) (Figure 3).

The first evidence for lactate production and oxidative disposal of lactate on working muscle was generated on dog gracilis and gastrocnemius muscle preparations (Connett et al., 1990; Jöbsis and Stainsby, 1968; Stainsby and Welch, 1966) and subsequently in working human muscles (Bendahan et al., 2017; Richardson et al., 1998). In muscles and arterial blood of resting healthy humans, lactate concentration approximates 1.0 mM, while pyruvate concentration approximates 0.1 mM, the L/P ratio being 10 (Henderson et al., 2007). In this resting state, net lactate production and release from resting muscle of healthy individuals (Bergman et al., 1999b; Stanley et al., 1986) occurs when intramuscular partial pressure of oxygen (PO_2) approximates 40 Torr (Richardson et al., 1998), well above the critical mitochondrial PO_2 for maximal mitochondrial respiration (1–2 Torr) (Bendahan et al., 2017; Rumsey et al., 1990). During exercise at about 65% of maximal oxygen consumption (VO_2max), net lactate production and release from working muscle beds rise with a corresponding increase in L/P more than an order of magnitude (to ~500), but the intramuscular PO_2 remains at 3–4 Torr, well above the critical mitochondrial O_2 level (Bendahan et al., 2017; Richardson et al., 1998). Hence, it is appropriate to conclude that in healthy humans glycolysis proceeds to lactate under fully aerobic conditions, as it must because the K_{eq} of lactate dehydrogenase (LDH) approximates 1,000 (Rogatzki et al., 2015). Importantly, most lactate (75%–80%) is disposed of immediately within the tissue or subsequent to release and reuptake by working muscle (Bergman et al., 1999b; Stanley et al., 1986), with significant uptake and oxidation by heart (Bergman et al., 2009; Gertz et al., 1988), brain (Glenn et al., 2015b; van Hall et al., 2009), and liver for gluconeogenesis (Bergman et al., 2000; Emhoff et al., 2013b; Stanley et al., 1988). Characterization of lactate as a dynamic fuel, produced even when oxygen is not lacking, redefines this molecule from being an apparent nuisance physiologically to being of metabolic benefit. Similarly, as discussed below, views have evolved over the years regarding the role of lactate (and/or associated protons) in causing muscle fatigue.

Lactate and Fatigue

Working with electrically stimulated but unperfused and non-oxygenated frog preparations, early researchers observed that muscle contraction was associated with lactic acid accumulation (Fletcher, 1907; Hill, 1914; Hill and Lupton, 1923; Meyerhof, 1920). Subsequently, in human experimentation, early investigators associated fatigue with limitations in oxygen supply (Hill and Lupton, 1923), and fatigue from high-intensity exercise consistently produces results of high [lactate] and proton accumulation (reduced pH) (Bangsbo et al., 1993; Sahlin et al., 1976); the traditional conclusion has been that lactic acid causes muscle fatigue. In relating lactate accumulation and fatigue, one might wonder why early and more recent investigators of physiology didn't conclude that lactate production was a means to ward off fatigue.

Because of the central role of lactate in intermediary metabolism and exercise performance, investigators in muscle and exercise physiology have made serious effort to distinguish between the separate effects of lactate anions and hydrogen ions on muscle performance. At present it is appropriate to conclude that exercise causes lactate anion and proton accumulation. However, it is unclear whether glycolysis makes lactic acid or if accumulated lactate anions and protons are derived from the same sources. It is also unclear if these compounds (lactate and hydrogen ions), individually, separately, or in aggregate, are causes of muscle fatigue *in vivo*. And even if lactatemia and decreased muscle and blood pH are fatigue agents, certainly they are not the only causes of fatigue (Fitts, 1994).

In considering the effect of lactate anion on muscle function, Allen and Lamb (Allen et al., 2008) reviewed results of their

own studies as well as the literature on the subject. Consequently, they could not accept the hypothesis that lactate anion accumulation caused muscle fatigue. Indeed, we now know that compared to glucose or fructose (Jeukendrup et al., 2006), oral consumption of arginyl lactate can improve exercise performance (Azevedo et al., 2007). Similarly, we now know that vascular sodium-lactate infusion provides an energy substrate, spares glucose, and has a slightly alkalizing effect on blood pH (Miller et al., 2002a, 2002b, 2005). Further, in the clinical setting it has been noted that vascular lactate infusion can improve cardiac performance in heart failure (Nalos et al., 2014). If the data on a fatigue effect of lactate anion are unconvincing, what then about the potential effect of hydrogen ion on muscle performance?

In terms of isolated muscle models of fatigue, results of recent reports and a review on the subject support the conclusion that the combined effects of acidosis, phosphate ion accumulation, and low Ca^{2+} (Debold et al., 2016) (as occurs in fatigue) interfere with cross-bridge cycling and hence muscle performance. However, those results and interpretations based on isolated muscle models are to be considered alongside those of de Paoli and colleagues (de Paoli et al., 2007), who showed that the addition of lactic acid and adrenaline to isolated, electrically stimulated rat soleus muscles increased excitability and relieved fatigue. In those experiments, a rise in extracellular K^+ due to release during excitation-coupling or added KCl caused disruption of the cell membrane electrical gradient that was corrected by the addition of lactic acid to the preparation. Hence, at present it is uncertain that proton accumulation during human muscle exercise is a major cause of muscle fatigue.

Now, with the benefit of almost a century of experimentation, we know that glycolysis is a means to produce ATP that allows cellular work to progress. Importantly, an accepted concept is that glycolysis is beneficial because it yields ATP (2 mol ATP/mol glucose and 3 mol ATP/mol glucosyl subunit of glycogen). As well, glycolysis produces lactate, an oxidizable substrate that downstream gives rise to a rich supply of ATP (Brooks, 1985). Fairly recently also, the idea has been advanced that glycolysis is pH neutral because it produces lactate anion, as opposed to lactic acid (Hochachka and Mommsen, 1983; Robergs et al., 2004). For instance, consider the terminal step in glycolysis catalyzed by LDH: pyruvate$^-$ anion + NADH + H^+ → lactate$^-$ anion + NAD^+; acid is not produced, but to the contrary, is removed, with a total accounting of the path from glucose to lactate being pH neutral and from glycogen to lactate being slightly alkalotic (Robergs et al., 2004). Hence, as suggested originally by Hochachka and Mommsen and supported by the accounting of Robergs et al., it is uncertain whether glycolysis produces lactate or lactic acid; they would argue for the former.

The idea that glycolysis does not produce acid has been challenged (Boning and Maassen, 2011; Gladden, 2008), largely because Robergs et al. could not explain where protons came from during physical exercise that stimulates glycolysis. The explanation of Robergs and colleagues, that ATP hydrolysis was the source of protons during exercise, is considered untenable because working muscle [ATP] is homeostatic. However, the criticism of Robergs et al. is perhaps not completely justified, because the source of protons in muscle contraction is unknown and the effects of muscle proton production on muscle and blood pH are not clear (Lindinger and Heigenhauser, 2008). To reiterate from above, according to the Stewart approach, blood pH is a dependent variable influenced by PCO_2, the concentration of weak acid buffers, and the strong ion difference.

Perhaps the strongest data that glycolysis produces protons and lactate anions on a 1:1 basis comes from Marcinek et al. (2010), who measured proton and ATP concentration changes in an ischemic mouse muscle model using ^{31}P-MRS and lactate anion accumulation biochemically. In the ^{31}P-MRS method, proton formation is determined from splitting of the phosphate peak, making the measurement critically important for determining muscle energetics from MRS. With no observed change in [ATP] in the muscle preparation, the data of Marcinek et al. indicated that proton generation agreed closely with the increases in lactate anions over the course of the ischemic period. Hence, their data supported a 1:1 stoichiometry between lactate and proton generation. However, while the experimental paradigm could measure protons, the source of those protons was not identified. Further, the experimental paradigm is less than ideal, and results are inconsistent with observations of lactate anion and proton accumulation in and release from working skeletal muscles that do not show the 1:1 lactate anion:proton ratio (Bangsbo et al., 1993, 1996, 1997; Juel et al., 1990).

In summary on this section, after a century of effort, what can we conclude on the interrelationships among cell work (e.g., muscle contraction), glycolysis, lactate, and proton accumulation? We can conclude that cell work stimulates glycolysis and also lactate anion and proton formation, but there is persistent controversy over whether glycolysis produces lactate or lactic acid. Further, there is similar controversy over whether either lactate anion or proton accumulation interferes with the mechanism of muscle contraction and causes fatigue. Certainly, glycolysis is necessary for muscle power generation, and certainly also lactate provides a fuel energy source. As well, results of the work of de Paoli et al. (2007) can be interpreted to mean that lactate and lactic acid prevent extracellular K^+ accumulation from interfering with action of Na^+ channels in working muscle. In sum, as implied in proponents of the maximal lactate steady state (Hofmann and Pokan, 2010), it can be concluded that rising lactate and falling pH in working muscle give evidence of disturbances to metabolic and acid/base homeostasis in working muscle that lead to termination of effort. To exemplify the complexity of the relationship between physical work capacity, lactate concentration during exercise, and fatigue, the case of high altitude exposure is discussed below.

Lactate at Altitude, the Lactate Paradox

When confronting the physiological stresses of high altitude exposure, early investigators noted that blood [lactate] was elevated at rest and during submaximal exercise intensities (Reeves et al., 1992). The natural thinking at the time was based on O_2 debt theory and the assumption that a deficit in oxygen consumption, i.e., a "Pasteur effect," was responsible for the elevation in circulating [lactate]. The term "Pasteur effect" for a stimulation in glucose use due to a limitation in O_2 supply is attributable to Warburg (Warburg, 1926), who drew a contrast between glucose use and lactate production in normal and cancer cells that consumed glucose and produced lactate regardless of the availability of oxygen (Warburg et al., 1927).

However, the assumption of a Pasteur effect in men working at altitude is untenable, because pulmonary oxygen consumption rate at altitude is the same as at sea level for a given power output. As well, early investigators were perplexed to discover that blood lactate accumulation after maximal effort was lower at altitude than at sea level. Still, the setting of high-altitude research has provided an outstanding opportunity to understand physiology and metabolism. Because of inconsistencies between observed results in men exercising at altitude and results anticipated based on assumption of a Pasteur effect, early investigators deemed the inconstancies to be paradoxes.

Now, based on isotope and limb balance studies, we know that acute exposure to high-altitude hypoxemia results in sympathetic activation that raises blood epinephrine (Mazzeo et al., 1995) and consequently lactate turnover in resting men and those engaged in exercises at given exercise power outputs (Brooks et al., 1998). From the same experiments, we now know also that the sympathetic response to altitude is blunted with acclimation such that blood epinephrine, [lactate], and lactate Ra are reduced compared to acute exposure, but not compared to sea-level normoxic exposure. Therefore, one "lactate paradox" at altitude is related to the effects of epinephrine in determining lactate production and hence blood Ra.

Referred to above is the paradoxical finding of a lower rather than higher blood lactate concentration on maximal exertion at altitude compared to sea level. This phenomenon is attributable to greatly reduced exercise power outputs at altitude. Reduced muscle work requires less glycolysis that results in lower lactate production and blood Ra.

And finally, still another lactate paradox observed in altitude sojourners is that while hypoxia and hypoxemia persist after acclimation, blood [lactate] is lower than on acute exposure while lactate Ra is greater than at sea level (Brooks et al., 1991a). The increased lactate Ra after acclimation is due to an increased dependence on glucose relative to sea level (Brooks et al., 1991b) and improved lactate clearance relative to acute altitude exposure (Brooks et al., 1991a).

Energetics of Lactate Production

It is safe to state that glycolysis is the entry pathway for catabolism of products of carbohydrate digestion (Brooks et al., 2005). Substrate-level phosphorylation of glucose yields a net of 2 ATP/mol of glucose, and assuming a ΔG of -11 kcal/mol for ATP, glycolysis yields -22 kcal/mol of glucose. Subsequently, continued catabolism of monocarboxylates (pyruvate and lactate) from glucose through the mitochondrial tricarboxylic acid cycle (TCA) and electron transport chain (ETC) yields an additional 32–34 mol ATP/mol glucose (Brooks et al., 2004). Overall, the oxidative catabolism of carbohydrate moieties yields $\approx$4 kcal/g, or 34–36 mol ATP/mol glucose (Brooks et al., 2004). As well, in terms of energetics, glycolysis is important for non-oxidative ("glycolytic" or "anaerobic") power production (Brooks, 2012).

Among the several functions of glycolysis, perhaps most notable is that the process engenders both sustained, oxidative and short-term, glycolytic high muscle power output activities. There are two modes of glycolytic function during exercise: (1) continuous glycolysis with lactate production (Ra) matched by oxidative disposal (Rd) and (2) accelerated glycolysis in which lactate Ra far exceeds the capacity of lactate Rd via oxidation, leading to profound lactate accumulation in muscle and blood (lactatemia). Sustained muscular power output depends on highly integrated processes involving cardiopulmonary, cardiovascular, and muscle oxidative capacities (Brooks, 2012, 2014). By way of comparison, a healthy young woman or man with a VO_2max of 3 L O_2/min with respiratory quotient (VCO_2/VO_2) $\approx$1.0 (indicting dependence on carbohydrate [CHO] combustion) generates 15 kcal/min from oxidative metabolism. Because the body's efficiency of converting chemical to mechanical power approximates 25% (Gaesser and Brooks, 1975), in the example provided the person could generate an external PO of $\approx$262 W (assuming 1 kcal/min = 69.8 W) through cell respiration. Unique individuals in the population with extraordinary levels of VO_2max (e.g., 5 L O_2/min) can generate proportionately higher levels of energy release (e.g., 20 kcal/min $\approx$1,400 W) from cell respiration. Because training and experience do not significantly affect muscle efficiency (Nickleberry and Brooks, 1996; San-Millán and Brooks, 2018), the external power output from cell respiration in the example cited would be only 350 W. However, we know from studies on athletes that they can generate much higher muscle power output during short periods of activity owing to the very high capacity for muscle glycogenolysis and glycolysis (di Prampero, 2003; Driss and Vandewalle, 2013; San-Millán and Brooks, 2018).

An example of sustained muscle activity in which glycolytic flux was matched to lactate Rd without lactatemia is to be found in a recent study on 22 International Cycling Union (ICU) male Pro Tour cyclists. With VO_2max normalized to body mass of 74.1 ± 4.7 mL O_2/kg/min and a maximal exercise power output of 378.5 ± 30 W, the Pro Tour cyclists could sustain exercise power outputs $\geq$ 300 W before significant lactatemia (San-Millán and Brooks, 2018). In contrast, corresponding values in moderately active, healthy young males were VO_2max 49.6 ± 5.8 mL O_2/kg/min and maximal leg power output 246.3 ± 26 W. Those men could generate only 125 W before lactatemia occurred. Rephrased, healthy young men could not even briefly achieve the muscle power output sustained by Pro Tour athletes for hours on consecutive days for weeks. The point of this illustration is that an individual's ability to sustain glycolysis and simultaneous lactate clearance without incurring hyperlactatemia is necessary for muscle power and endurance in athletics and other endurance activities.

In contrast to the example of Pro Tour cyclists capable of matching glycolytic flux and oxidative lactate disposal over sustained periods is the example of power athletes. Power athletes are capable of bursts of muscle power measured not in W, but in kilowatts (kW) (di Prampero, 2003; Driss and Vandewalle, 2013). During high-power activities, ATP and creatine phosphate (CP) stores in muscle are readily and rapidly available but meager (10–12 kcal) (Brooks et al., 2004). Oxygen stores in blood and muscle combined with a few breaths of O_2 consumption can provide some ATP, but most energy must come from glycogenolysis and glycolysis. Proportions used by the three energy sources are time dependent, with CP consumed in the first seconds and energy contributions from glycolysis and cell respiration growing in importance as duration extends. Because the half response time for oxygen consumption approximates 30 s, the message is that glycolysis is essential for high muscle power as in sprint

activities. Glycolysis provides ATP directly by substrate level phosphorylation of ADP and indirectly by providing lactate and pyruvate as substrates for mitochondrial oxidative phosphorylation.

Body Fueling with Lactate Compared to Glucose

Compared to glucose flux that may increase 2–3 times in humans during the transition from rest to exercise (Bergman et al., 1999a; Emhoff et al., 2013b; Friedlander et al., 1997, 1998; Stanley et al., 1988), the capacity to increase lactate flux is far more expansive, rising from a rate 50% of that of glucose in a resting postabsorptive person to a value four times that of the glucose flux during exercise (Bergman et al., 1999b; Brooks et al., 1991a; Mazzeo et al., 1986; Stanley et al., 1985, 1986, 1988). In rodents with relatively high metabolic rates, lactate flux can exceed glucose flux in resting animals, but again, the many-fold gain in lactate over glucose flux is seen in the transition from rest to exercise (Brooks and Donovan, 1983; Donovan and Brooks, 1983). In terms of fueling active tissues during exercise, it is important to recognize that 80% or more of lactate is disposed of via oxidation (Bergman et al., 1999b; Mazzeo et al., 1986; Stanley et al., 1986). To a physiologist, the relatively greater gain in lactate over glucose flux capacity is readily appreciated because hepatic glycogenolysis and muscle glycogenolysis rates are very low in resting postabsorptive conditions (Ahlborg and Felig, 1982). However, despite a rise in hepatic glycogenolysis supporting glucose Ra during exercise, the massive increases in muscle glycogenolysis during exercise (Bergström and Hultman, 1967; Hultman, 1967) give rise to glycolysis and muscle lactate production (Bergman et al., 1999b; Stanley et al., 1986) that dwarf the capacity for hepatic and renal glucose Ra and muscle glucose uptake. This use of lactate as a fuel requires mitochondrial respiration, and thus it follows that an ability to rapidly utilize lactate (or any other oxidation fuel) requires ample mitochondrial abundance and respiratory capacity. The body has evolved to couple lactate supply and capacity for utilization through regulation of mitochondrial biogenesis that is discussed below.

Mitochondrial Biogenesis and Lactate

Modern studies in physiology and biochemistry have shown that remarkable plasticity of the mitochondrial abundance in response to regular, endurance-type physical activity as well as high-intensity interval training (HIIT) may double the mitochondrial mass (Davies et al., 1981; Holloszy, 1967; Kirkwood et al., 1987; Robinson et al., 2017). Contemporary studies of physiology and biochemistry have also revealed the molecular signals for exercise-induced increases in mitochondrial protein expression. Among the cellular signaling candidates for transcriptional control of mitochondrial biogenesis are: calcium ion (Ojuka et al., 2002), AMP-activated protein kinase (AMPK) (Luo et al., 2005; Wadley et al., 2006), Sirtuin 1 (Sirt1) (Dumke et al., 2009), and the "master mitochondrial biogenesis activator," peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) (Handschin and Spiegelman, 2011). Downstream regulators of mitochondrial biogenesis are: nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) and mitochondrial transcription factor A (TFAM) (Nirwane and Majumdar, 2017). What these signaling pathways appear to share in common are circumstances resulting from a challenge to ATP homeostasis (Brooks, 2010, 2014, 2016).

While there has been major emphasis in studying downstream effectors of mitochondrial biogenesis, scarce attention has been placed on upstream effectors. For instance, Lezi and colleagues in the Swerdlow lab (E et al., 2013) have shown that intraperitoneal L-lactate administration to mice upregulates mitochondrial protein expression in diverse tissues such as brain. This upregulation of mitochondrial protein expression is perhaps best exemplified in the effort to identify how changes in Sirt1 activation affect mitochondrial biogenesis. In diverse reports on SIRT 1, activation was observed via changes in cell redox through putative roles of the concentration of nicotinamide (NAM) and the activity of enzyme NAM phosphoribosyl transferase (Nampt). However, what is lacking is a comparison of how changes in Nampt activity versus changes in glycolytic flux and attendant lactate production and disposal can change cell redox *in vivo*. Similarly, what is lacking is a comparison of how lactate production and attendant changes in cytosolic redox in driver cells and disposal in recipient cells affects the NAD^+/NADH in various cell compartments. Nominal [lactate] in cells is < 1.0 mM, but the dynamic range in flux and concentration can be 20- to 30-fold (Cheetham et al., 1986), with a corresponding dynamic L/P range of 10 to > 500 (Henderson et al., 2007). The rise in blood L/P during exercise is relatively larger than the relative rise in [lactate] because the relative and absolute increments in [pyruvate] are low compared the comparable changes in [lactate] (Henderson et al., 2007; Wasserman et al., 1985). Interestingly, based on simultaneously determined values of L/P in the venous effluent from working muscle and arterial blood, it is evident that ratios are much lower in arterial than in venous blood. These results are attributable to pulmonary lactate clearance and indicate a role for the lungs as a metabolic organ (Johnson et al., 2011, 2012). Regardless of relative or absolute changes in blood lactate and pyruvate levels during a single circulatory passage, the impactful role of lactate in cell-cell signaling is indicated by the presence of millimolar changes in lactate concentration and order-of-magnitude changes in L/P that are to be contrasted with nano- or femtomolar changes in the concentrations of transcription factors and coactivators in response to exercise and other stresses.

Gluconeogenesis from Lactate

Because the majority of lactate disposal is directed toward immediate oxidation, the bulk of the discussion on lactate utilization above centered around oxidative disposal. However, perhaps the first recognition of a metabolically beneficial use of lactate in normal physiology was discovery of the Cori cycle, with lactate as the major gluconeogenic precursor (Cori and Cori, 1946). Indeed, in addition to acting as an oxidative fuel source, lactate flux is metabolically beneficial through its supplying carbon to gluconeogenesis. As typically rendered, the Cori cycle is depicted as having intracellular lactate shuttles in both muscle and liver that are linked via a cell-cell or rather an organ-organ (muscle to liver) lactate shuttle. Although developed on the basis of elegant studies on laboratory animals, due to technical limitations the Coris, in fact, never demonstrated the phenomenon in humans. Still, with contemporary isotope tracer and arterial-venous difference measurements, it is certain that glycemia is supported during postabsorptive (fasted) rest and physical exercise (Bergman et al., 2000; Consoli et al., 1990; Emhoff et al., 2013b; Friedlander et al., 1997, 1998; Jenssen

et al., 1993; Woerle et al., 2003) and that hepatic gluconeogenic function is augmented by the kidneys under diverse physiological conditions (Meyer et al., 2002a, 2002b).

Lactate Shuttling in Postprandial Glycogen Repletion: The "Glucose Paradox"

The importance of lactate in intermediary metabolism is also illustrated by its central role in the "glucose paradox." In postabsorptive conditions, lactate is the main gluconeogenic precursor (Bergman et al., 1999a, 2000; Emhoff et al., 2013b; Meyer et al., 2002a; Trimmer et al., 2002; Woerle et al., 2003). However, the path of carbon from dietary cerebral carbohydrate (CHO) to hepatic glucose and glycogen is indirect. After a CHO-containing meal, a significant portion of glucose from digestion bypasses the liver, and glycolysis and lactate production are stimulated in peripheral tissues (e.g., muscle) (Brooks, 1997, 1998, 2012). Via muscle efflux and systemic delivery, lactate provides the precursor for hepatic glycogen synthesis via the "indirect pathway" (Foster, 1984). The pathway is referred to as "indirect" and "paradoxical" because some hepatic portal glucose from CHO nutrition bypasses the liver and enters the systemic circulation only to return as a precursor (lactate) for glycogen synthesis. Estimates vary depending on species, but the relative indirect pathway contribution to postprandial hepatic glycogen synthesis in humans (≈25%) (Woerle et al., 2003) is less than in animal models, but still appreciable (Foster, 1984). Hence, from the perspective of the indirect pathway of hepatic glycogen synthesis, a rise in arterial blood [La^-] following CHO ingestion stimulates glyconeogenesis and the fraction of gluconeogenesis derived from lactate.

Brain Function, Cognition, and Lactate

As early as the 1950s, Henry McIlwain had shown that lactate is an efficient fuel for the brain *ex vivo* (McIlwain, 1953). This finding has received decades of supporting evidence from Schurr and others (Schurr and Gozal, 2012; Schurr and Payne, 2007). On a net basis, in resting, postabsorptive individuals, glucose is the preferred fuel source for the brain. Net cerebral uptake (i.e., cerebral metabolic rate, CMR) for glucose depends on cerebral blood flow (CBF) and the arterial-venous [glucose] difference (CMRGlucose = (a−v) Glucose (CBF)). In most cases, in resting individuals, delivery of glucose to the brain (blood [glucose] approximating 5 mM and 180 g/mol) is large compared to the corresponding values for lactate (blood [lactate] < 1.0 mM and 89 g/mol). Hence, in resting postabsorptive individuals, lactate's contribution to brain fueling is low compared to glucose. For example, at a plasma [lactate] of 1.0 mM, on a net basis, lactate contributes to 8%–12% of the brain's total energy requirement (Gallagher et al., 2009; Glenn et al., 2015b). However, if one evaluates the importance of brain fueling simply by considering net metabolite uptake, then the role of lactate in brain fueling will not be appreciated. Two types of cases appropriately describe the importance of lactate in brain fueling; these examples are after traumatic brain injury (TBI) and physical exercise by healthy individuals.

In comatose TBI patients, the role of lactate in brain fueling was found to be impressive, as most (70%–80%) of circulating blood glucose was produced via gluconeogenesis from lactate (Glenn et al., 2015a, 2015b). As well, net lactate uptake provided 12% of brain fuel. Hence, indirectly via gluconeogenesis (45%), plus directly (12%), most (57%) of brain fuel was from lactate.

In healthy humans during exercise, plasma lactate levels can increase an order of magnitude or more. For example, with a 10-fold rise in concentration, net lactate uptake provided 25% of total brain energy need (Gallagher et al., 2009; van Hall et al., 2009). Neglecting for a moment that cerebral disposal of glucose is by conversion to lactate, preference of cerebral lactate over glucose is seen in studies on rats (Smith et al., 2003) and humans (Quistorff et al., 2008; van Hall et al., 2009), and the provision of lactate to a healthy brain decreases glucose net uptake. This observation indicates an important cerebral lactate shuttling phenomenon. Alternatively, some might consider that lactate can serve as an "alternative brain fuel." However, as emphasized by Schurr, lactate is "the brain fuel" because whether extracellular glucose or lactate are taken up by brain, the path of glucose disposal is through conversion to lactate and a cell-cell lactate shuttle (Schurr, 2006; Schurr and Payne, 2007).

In addition to serving as a cerebral energy substrate, circulating lactate can signal secretion of cerebral brain-derived neurotrophic factor (BDNF). As already discussed in part, circulating blood lactate can be raised during exercise by production in muscle, the integument, and other epinephrine-sensitive tissues. As well, circulating lactate levels can be raised during rest or exercise by vascular L-lactate infusion into the systemic circulation. Indeed, infused sodium lactate raises circulating BDNF levels (Coco et al., 2013). BDNF is a member of the neurotrophic family of proteins and facilitates neurogenesis, neuroprotection, neuroregeneration, and synaptic plasticity as well as formation, retention, and recall of memory (Seifert et al., 2010). BDNF is produced both in the central nervous system and in other tissues, including the vascular endothelium. High levels of BDNF mRNA are found in the hippocampus and in the cerebral cortex, and in rodent models physical exercise is the strongest known stimulus to BDNF expression in the hippocampus (Cotman and Berchtold, 2002). In contrast, attenuated expression of BDNF mRNA in the hippocampus may constitute a pathogenic factor common to Alzheimer's disease and major depression (Tsai, 2003). Circulating BDNF is typically elevated in exercise, but levels are reduced in patients with depression and type 2 diabetes (Krabbe et al., 2007). Even though acute exercise increases BDNF production in the hippocampus and cerebral cortex, studying the effects of exercise on BDNF expression in the human brain is difficult. In what may become noted as a classic study in neurochemistry, Seifert et al. (Seifert et al., 2010) compared BDNF levels in arterial and internal jugular vein blood and showed effects of exercise and exercise training on cerebral BDNF net release.

While many posit a positive role for BDNF in terms of cognition, it is important to know also that lactate therapy has been shown to raise BDNF levels and improve cognitive function in rodent models following brain injury (Bisri et al., 2016; Holloway et al., 2007; Rice et al., 2002). Most recently, in an extraordinary set of experiments on healthy men who volunteered to exercise at high intensities with arterial and jugular bulb catheters in place, Hashimoto et al. (Hashimoto et al., 2018) showed that executive function was directly correlated to blood [lactate] and cerebral lactate uptake. Most recently, Wang et al. (Wang et al., 2017) provided data that optogenetic activation of astrocytes in the anterior cingulate cortex (ACC) triggers lactate

release and improves decision-making in rats with chronic visceral pain. Hence, as predicted in papers from studies on rodents (Schurr and Gozal, 2012; Wang et al., 2017) and healthy and injured humans (Glenn et al., 2015b), Hashimoto et al. produced results that brain fueling with lactate improved cerebral functioning. Additionally, with respect to cognition, it has been shown that long-term memory consolidation in rat hippocampus relies on lactate and the ANLS (Steinman et al., 2016; Suzuki et al., 2011).

L- versus D-Lactate Enantiomer

The use of lactate-containing solutions and supplementation of energy in clinical settings (i.e., hospital resuscitation fluids) will be discussed later. However, before leaving this introductory section, it is important to note that it is the L- (not the D-) lactate enantiomer that possesses physiological action and efficacy for energy supplementation and cell signaling in resuscitation fluids. Several lines of evidence support this statement.

Early studies on transporter-mediated lactate movement across plasma membranes clearly indicated Michaelis-Menten kinetics and stereospecificity of L-lactate transport. In contrast, exchange of D-lactate was far slower and did not follow Michaelis-Menten kinetics or display other characteristics of carrier-mediated transport (Garcia et al., 1994; Roth and Brooks, 1990a, 1990b). As well, evidence points to L-lactate as the effective enantiomer in fluid resuscitation (Boysen and Dorval, 2014; Chan et al., 1994; de-Madaria et al., 2017). Additionally, L-lactate is the ligand for the putative lactate receptor GPR81 that is expressed in brain, muscle, and adipose tissues (Ahmed et al., 2010; Bergersen, 2015; Lauritzen et al., 2014). As an aside to reappear later in this review, clinicians tend to use either "normal" (0.9%) NaCl or Lactated Ringer's (273 mOsm) solutions for fluid resuscitation. However, while administration of either is consistent with Standard of Care (SOC) fluid resuscitation, until recently it was unclear from the literature whether one or the other solution results in superior patient outcomes (de-Madaria et al., 2017). Rather, the selection of one solution over the other seems more to do with tradition in clinical training rather than laboratory or clinical science. Perhaps the absence of clear superiority of Lactated Ringer's solution compared to normal saline has to do with inclusion of racemic mixtures containing equal contents of D- and L-lactate enantiomers in Lactated Ringer's solutions?

Neither from the classic or contemporary literature nor from vendor specifications on FDA-approved products is it clear whether commercially approved and clinically used Lactated Ringer's solutions contain 100% L-lactate or a racemic (50/50) mixture of L- and D-lactate, a disadvantage of the D-lactate enantiomer, being that it is neurotoxic (Chan et al., 1994). Although not FDA approved by virtue of extensive clinical trials, in clinical experiments we (Miller et al., 2002a, 2002b, 2005) and others (Bouzat et al., 2014) have administered isotonic (310 mM) and hypertonic (0.5 M) sodium L-lactate solutions with good effects in published reports and ongoing clinical trials (*vide infra*).

The Cell-Cell Lactate Shuttle: Initial Discovery

The initial impetus leading to recognition of the presence of a "lactate shuttle" came by means of an invitation from the distinguished comparative physiologist Peter Hochachka to participate in a symposium on "The Biochemistry of Exercise: Insights from Comparative Studies" to be held in Liege, Belgium in 1984. Recognition of the presence of lactate shuttling in normal physiology has led to discovery of the presence of several lactate shuttles. Piecing together recently published data on glucose (Brooks and Donovan, 1983) and lactate (Donovan and Brooks, 1983) fluxes in resting and exercising trained and untrained rats with other data on lactate concentrations and fluxes in mammals, the concept of a lactate shuttle emerged. In terms of quantitation, lactate turnover and oxidation in resting rats were surprisingly high, but typically less than corresponding glucose flux rates. However, during exercise lactate flux and oxidation easily exceeded glucose flux rates. Moreover, during exercise most glucose production came from lactate via gluconeogenesis (the Cori cycle). In terms of the effects of training on carbohydrate metabolism, training not only increased the capacity of gluconeogenesis, but training had dramatic effects on lactate metabolic clearance rate (MCR = disposal rate/concentration). The classic effect of exercise training to lower blood lactate concentration was observed in rats running on a motorized treadmill, but tracer data showed that lactate production was high but balanced by disposal in exercising trained rats, the lower circulating blood lactate concentration being explained by greater clearance rates attributable to increased oxidation and gluconeogenesis of lactate (Brooks and Donovan, 1983; Donovan and Brooks, 1983). Subsequently, with the advent of stable, non-radioactive isotope tracers, the same effects of training on glucose and lactate turnover responses to exercise and exercise training were replicated in cross-sectional (Emhoff et al., 2013a, 2013b; Mazzeo et al., 1986; Stanley et al., 1985) and longitudinal training studies on humans (Bergman et al., 1999a, 1999b, 2000).

Results of whole-body tracer studies are informative, but the data provided no specific data on the tissue sites of lactate production and disposal. However, in 1984 studies on tissue specificity of lactate metabolism were underway (Bergman et al., 1999b; Gertz et al., 1981; Stanley et al., 1986), and more were to come later (Bergman et al., 1999a, 1999b; Gertz et al., 1988). For example, in 1984 fueling of the heart during exercise with lactate released from working muscle beds was observed and was key to envisioning a lactate shuttle. As well, from studies by Paul Mole, Kenneth Baldwin, and their associates on muscles of lab rats made to exercise acutely and chronically (Hooker and Baldwin, 1979; Molé et al., 1973), a lactate shuttle concept was necessary to explain not only why lactate concentration in working red skeletal muscle was lower than that in white sections of the same muscle, but also why lactate concentration in working red skeletal muscle was lower than that in the blood perfusing it. Thus, the concept of a lactate shuttle was born (Brooks, 1984) and subsequently described more fully (Brooks, 1985, 1986). In terms of cell-cell lactate shuttling, it was subsequently recognized that red and white fibers exchange lactate within a tissue bed and between tissue beds such as skeletal muscle and heart. The beating heart takes up and oxidizes lactate (Bergman et al., 2009; Gertz et al., 1981, 1988), as do working skeletal muscle beds (Bergman et al., 1999b; Stanley et al., 1986), but what is the path between lactate uptake and the formation and release of CO_2 from a tissue bed? Was there an intracellular lactate shuttle?

Intracellular Lactate Shuttles

The Cytosol-to-Mitochondrial Lactate Shuttle and Mitochondrial Lactate Oxidation Complex (mLOC)

Historically, many believed that the liver and kidneys are the major organs of lactate disposal via gluconeogenesis (Cori and Cori, 1946) and conversion to bicarbonate (e.g., https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=2425), evidence for the purported conversion of lactate to bicarbonate in the liver being nil. In contrast, studies on humans (Mazzeo et al., 1986; Stanley et al., 1985) and other mammals (Depocas et al., 1969; Donovan and Brooks, 1983; Freminet et al., 1974) revealed that most lactate was disposed of via oxidation (to CO_2, with bicarbonate formed simply as the result of CO_2 reacting with water in an equilibrium reaction catalyzed by carbonic anhydrase). Lactate disposal via oxidation was particularly prominent when muscles were engaged. With that realization, issues arose: where in a working muscle, heart, or other tissue or cells was lactate oxidized? Much thinking was that the first step in lactate oxidation to pyruvate occurred in the cytosol, but for several reasons that idea made no sense. Beating heart (Gertz et al., 1981) and working red muscle (Stanley et al., 1986; Zinker et al., 1993) simultaneously consume glucose and take up and oxidize lactate. To reiterate, in arterial blood of a resting person, the lactate-to-pyruvate ratio (L/P) ranges from 10 (Henderson et al., 2007) to 20 (Wasserman et al., 1985); however, when muscles contract to achieve a moderate exercise power output, the L/P in venous blood effluent of working muscle rises more than an order of magnitude (i.e., L/P > 500) (Henderson et al., 2007). Because of the presence of LDH in erythrocytes and lung parenchyma (Johnson et al., 2011, 2012), relative rise of the L/P in arterial blood of exercising individuals is significant but blunted (Bergman et al., 1999b; Henderson et al., 2007; Wasserman et al., 1985). Given these data, the notion that lactate oxidation occurs in the cytosol is implausible. If not in the cytosol, where then does lactate oxidation commence? Where else but in the mitochondrial reticulum!

The thought process that lactate oxidation occurred in mitochondria stemmed from work using the classical enzymatic lactate analysis utilizing LDH (Gutmann and Wahlefeld, 1974). Realizing that the K_{eq} for LDH approximated 1,000, thus favoring the reduction of pyruvate to lactate and making lactate oxidation to pyruvate unlikely, Gutmann utilized hydrazine to trap pyruvate as hydrazone, thus keeping the concentration of pyruvate very low and allowing LDH to work against its natural equilibrium and oxidize pyruvate to lactate, an NAD^+/NADH-linked reaction, and allowing spectrophotometric detection. Hence, the pyruvate and lactate assays were similar, except that the assay for lactate contained hydrazine whereas the assay for pyruvate did not (Gutmann and Wahlefeld, 1974). With that knowledge, the analogous model became that the mitochondrial reticulum served as the pyruvate trap allowing mitochondrial LDH to oxidize lactate to pyruvate that would subsequently be rapidly cleared by PDH to keep pyruvate levels low and resulting in oxidation in the TCA cycle. This idea presupposed that the mitochondrial reticulum could oxidize lactate and that the reticulum contained an MCT and LDH, as well. It turned out that the model is correct.

The Mitochondrial Lactate Oxidation Complex (mLOC)

The discovery that mammalian mitochondrial preparations oxidize lactate has been controversial; some investigators can produce such preparations (Baba and Sharma, 1971; Brandt et al., 1987; Brooks et al., 1999a; De Bari et al., 2004; Kline et al., 1986; Passarella et al., 2014), whereas some (Rasmussen et al., 2002; Sahlin et al., 2002; Yoshida et al., 2007) cannot. With clear demonstration of lactate oxidation in mitochondrial preparations from human skeletal muscle (Jacobs et al., 2013) along with supportive data from magnetic resonance spectroscopy (MRS) (Chen et al., 2016; Park et al., 2015), perhaps the issue of mitochondrial lactate oxidation has been resolved? Difficulties in obtaining vesicular mitochondrial preparations from mammalian tissues likely have to do with disruption of the mitochondrial reticulum (Glancy et al., 2017; Kirkwood et al., 1986) during isolation and labiality and fragility of the L-lactate dehydrogenase during isolation of mitochondrial vesicles. Loss of a mitochondrial preparation's (Boussouar and Benahmed, 2004) capacity to respire lactate is not unique, as a similar problem with oxidation of long-chain fatty acids has been ascribed to use of the proteolytic enzyme Nagarse to increase mitochondrial protein yield, but the resulting preparations lose the ability to oxidize fatty acids or their carnitine derivatives (Pande and Blanchaer, 1970). In this instance the inability of mitochondria preparations to recapitulate what is known to happen *in vivo* can be ascribed to isolation artifact. Similarly, the ability or inability of mitochondrial preparations to oxidize exogenous lactate may be attributed to isolation artifact. Obviously, more work on issues related to mitochondrial isolation artifacts and the intracellular sites of lactate oxidation is required.

To the point, tissue lactate production, uptake, and oxidation occur because glycolysis and mitochondrial respiration occur simultaneously *in vivo*. For the mitochondrial reticulum to oxidize lactate, the reticulum must contain a transporter (Brooks et al., 1999a; Butz et al., 2004) and LDH (Baba and Sharma, 1971; Hashimoto et al., 2006), both of which were found as soon as probed for and are now listed in mitochondrial constituent databases such as MitoCarta (Calvo et al., 2016; Pagliarini et al., 2008) and MitoMiner (http://mitominer.mrc-mbu.cam.ac.uk/release-4.0/begin.do).

In terms of functionality, the mLOC (Figure 4) 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 (Hashimoto et al., 2006), liver (De Bari et al., 2004; Passarella et al., 2014), brain (Hashimoto et al., 2008), and various model systems such as brain slices (Schurr, 2008), primary neuronal cultures (Atlante et al., 2007; Hashimoto et al., 2008), normal breast and transformed breast cancer cells (Hussien and Brooks, 2011), and tumors (Sonveaux et al., 2008). But why does the model (Figure 4) not emphasize a role for the mitochondrial pyruvate carrier (mPC)? The answer is that definitive data are not available on spatial and functional interactions between mPCs and mMCTs and the role of mPCs in mitochondrial lactate oxidation.

Following reports of discovery of the mPC (Bricker et al., 2012; Herzig et al., 2012), and with access to our own custom antibodies to MCT1 as well as commercially available antibodies to the putative mPC, we obtained images assessing colocalization of MCT1 and mPC in L6 cells. In those preliminary studies, colocalization analysis of mMCT1 and mPC1 in Imaris software showed an r^2 of 0.8. It appears that both MCT1 and mPC are co-localized to the mitochondria (r^2 = 0.8). However, at the light

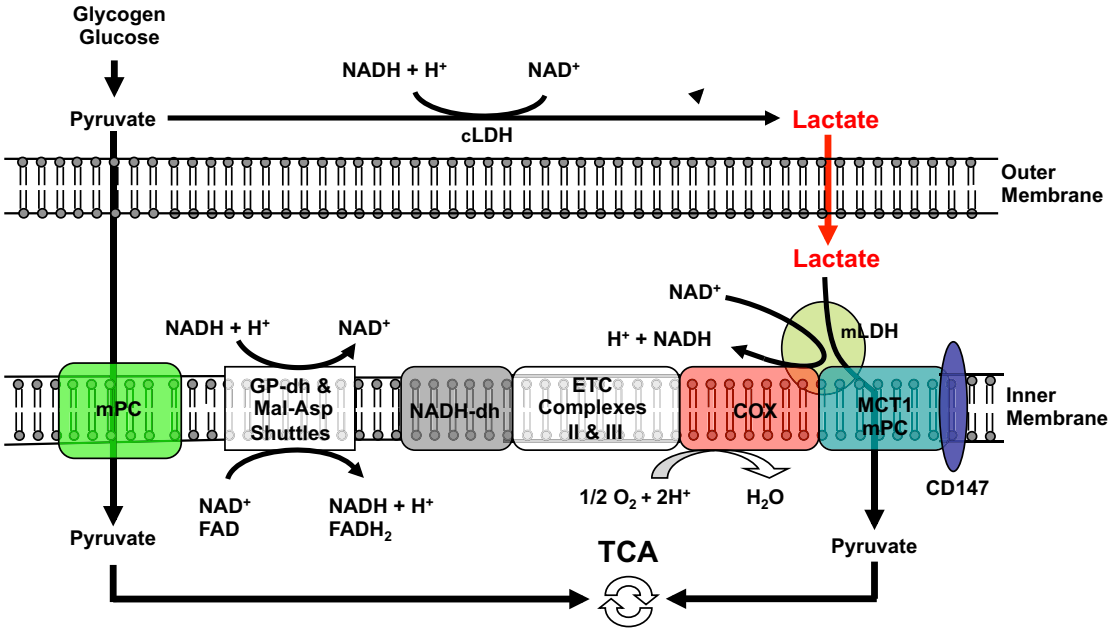

Figure 4. Mitochondrial Lactate Oxidation Complex

A schematic showing the putative mitochondrial lactate oxidation complex (mLOC): MCT1 is inserted into the mitochondrial inner membrane, strongly interacting with its chaperone protein CD147, and is also associated with COx as well as mitochondrial LDH (mLDH), which could be located at the outer side of the inner membrane. Lactate, which is always produced in cytosol of muscle and other tissues because of the abundance, activity, and characteristics of cytosolic LDH, is oxidized to pyruvate via the lactate oxidation complex in mitochondria of the same cell. This endergonic lactate oxidation reaction catalyzed by mLDH, is coupled to the exergonic redox change in COx during mitochondrial electron transport. GP, glycerol phosphate; Mal-Asp, malate-aspartate; ETC, electron transport chain; MCT, monocarboxylate (lactate) transporter; mPC, mitochondrial pyruvate carrier; mLDH, mitochondrial lactate dehydrogenase; TCA, tricarboxylic acid cycle. Redrawn from Hashimoto et al., 2006.

microscopic level, it is impossible to know if mMCT and mPC interact physically and functionally. Immunocoprecipitation, X-ray crystallography, mass spectrometry, and deletion studies are needed to definitively answer questions about mMCT and mPC colocalization and functionality and role of the mPC in mitochondrial lactate oxidation.

And finally, with regard to the site of intramitochondrial lactate oxidation to pyruvate, in an attempt to integrate ideas about the place of mPCs in mitochondrial morphometry (Divakaruni and Murphy, 2012), Gladden and associates (Rogatzki et al., 2015) modified Figure 4 to include a role for the mPC in mitochondrial lactate oxidation. That decision led to the hypothesis that mitochondrial lactate oxidation to pyruvate occurred in the mitochondrial inter-membrane space, but that conclusion is inconsistent with what we (Hashimoto et al., 2008; Hussien and Brooks, 2011) and others (Atlante et al., 2007; De Bari et al., 2004; Passarella et al., 2014) have found concerning the location of mitochondrial LDH.

Results of future research efforts to better define mitochondrial lactate and pyruvate oxidation complexes are greatly anticipated. Nonetheless, at present it is possible to conclude that the mitochondrial reticulum contains mechanisms to oxidize pyruvate and lactate as depicted in Figures 3 and 4.

By way of completeness, credit for use of the term "lactate shuttle" needs to be attributed to Nobuhisa Baba and Hari M. Sharma (Baba and Sharma, 1971), who in 1971 published histological evidence of LDH in rat heart and pectoralis muscle. In explaining the potential significance of their findings, they postulated the presence of a lactate shuttle. I discovered the 1971 reference after the same realization and years of research on the subject. In response to a letter of inquiry, asking why the shuttle hypothesis was not pursued, Nobuhisa Baba indicated that clinical responsibilities precluded further investigation.

The Peroxisomal Lactate Shuttle and β-Oxidation

Peroxisomes are cellular organelles found in virtually all eukaryotic cells that are involved in catabolism of substances such as very-long-chain (i.e., C22 and longer) fatty acids, branched-chain fatty acids, D-amino acids, poly amines, and reactive oxygen species such as hydrogen peroxide (H_2O_2) (Gladden, 2004). While it was known that β-oxidation of very-long-chain fatty acids occurred in mammalian peroxisomes (Lazarow and De Duve, 1976), in the absence of enzyme systems as exist in the mitochondrial matrix, it was not understood how β-oxidation could occur in peroxisomes. Key findings were that of Baumgart et al. (Baumgart et al., 1996), who showed the presence of peroxisomal LDH isoforms, and McClelland et al. (McClelland et al., 2003), who confirmed the presence of LDH and further demonstrated that rat liver peroxisomal membranes contained MCT1 and MCT2. From there it was possible to hypothesize that peroxisomal redox control necessary to support β-oxidation involved a lactate-pyruvate shuttle.

Other than demonstrating the presence of peroxisomal LDH (pLDH) and MCTs (pMCT), additional key findings were that peroxisomal redox was affected by the addition of exogenous pyruvate or the LDH inhibitor oxamate. As well, the addition of exogenous pyruvate gave rise to peroxisomal lactate production and efflux, and further, pyruvate-stimulated peroxisomal β-oxidation was inhibited by the MCT blocker, α-cyano-4-hydroxycinnamate

(CINN) (McClelland et al., 2003). Discovery of the peroxisomal lactate shuttle involving pyruvate-lactate conversion linked to changes in the NADH/NAD^+ redox couple emphasizes the critical importance of redox changes in all forms of lactate shuttles.

Other Lactate Shuttles and Other Roles of Lactate

Since recognition of the presence of lactate shuttling within and among various cells, tissues, and organs such as muscle, heart, and liver (Brooks, 1984, 1985, 1986, 2002), the concept has been extended to include other cells, tissues, and organs such as brain (Liu et al., 2017; Pellerin et al., 1998), lung (Johnson et al., 2011, 2012), sperm (Boussouar and Benahmed, 2004; Storey and Kayne, 1977), adipose (Ahmed et al., 2010; Cai et al., 2008; Liu et al., 2009), and peroxisomes (McClelland et al., 2003).

Astrocyte-Neuron Lactate Shuttle

Lactate shuttling between astrocytes and neurons was linked to glutamatergic signaling by Pellerin and colleagues in 1994 (Pellerin and Magistretti, 1994), but the significance of the findings and use of the term ANLS was to come some years later (Magistretti et al., 1999). Since its introduction and further exposition (Pellerin and Magistretti, 2012), the concept has remained controversial (Patel et al., 2014). However, realizing that lactate has autocrine-, paracrine-, and endocrine-like functions, the question should be, "How can there not be an ANLS?" Elegant studies, e.g., Pellerin et al., 2005, support the supposition that an ANLS was operant. However, while cerebral lactate flux may be related to glutamatergic signaling (Pellerin and Magistretti, 1994), there is no reason to suppose that other cerebral processes do not participate in lactate shuttling. For instance, in health and after injury, the brain takes up and oxidizes lactate from the systemic circulation (Glenn et al., 2015b) just as it does during physical exercise (Hashimoto et al., 2018; van Hall et al., 2009). In such cases, metabolism is more accurately described as a tissue-tissue, as opposed to a cell-cell (i.e., astrocyte-neuron) lactate shuttle. Regardless, the lactate shuttle concept holds true and explains the exchange between lactate producer (driver) and lactate recipient (consumer) cells in tissue-tissue and cell-cell lactate shuttles in brain, and elsewhere (Figure 1B).

Because characteristics of cellular lactate uptake such as stereospecificity, concentration and pH dependence, saturation, and inhibition by competitive and non-competitive inhibitors were recognized (Roth and Brooks, 1990a, 1990b; Watt et al., 1988) even before MCT isoforms were cloned and sequenced (Garcia et al., 1994, 1995; Price et al., 1998), it has been appreciated that while MCTs facilitate movement of monocarboxylates such as lactate, pyruvate, and acetoacetate across biological membranes, MCTs do not create the conditions for lactate exchange; rather, driver processes such as glycolysis and glycogenolysis give rise to lactate production, whereas recipient processes such as mitochondrial respiration and gluconeogenesis are responsible for lactate disposal (Brooks, 1984, 2002). Rephrased, MCTs facilitate lactate transport down concentration and pH gradients. In this context of hydrogen ion- and lactate anion-driven lactate flux, cerebral lactate exchange can be appreciated. Just as lactate release from working muscle (Stanley et al., 1986) can fuel the beating heart (Gertz et al., 1988), so too can working muscle fuel the brain (van Hall et al., 2009), an ANLS not being necessary to explain cerebral lactate metabolism as there is no obligatory role for astrocytes to generate lactate for consumption by neurons (Schurr, 2008). Examination of the cell type indicates that neurons possess the apparatus necessary for lactate production and release (Hashimoto et al., 2008) independent of an ANLS. Still, discovery of the ANLS has advanced the field of lactate shuttles substantially by providing a mechanism to describe cerebral physiology such as memory formation.

Lactate Shuttling and Lipolysis in Adipose

An inverse relationship between blood [La^-] and plasma free fatty acid concentration [FFA] and oxidation has long been recognized (Brooks and Mercier, 1994), but the associations are underappreciated. In the 1960s Bella Issekutz and colleagues noted the effect of lactacidemia on diminishing circulating [FFA] in individuals during hard exercise (Issekutz and Miller, 1962; Rodahl et al., 1964), and lactate infusion into running dogs caused circulating [FFA] to decline (Gold et al., 1963; Issekutz and Miller, 1962; Miller et al., 1964). In their work these investigators could clearly observe an effect of the lactate on circulating [FFA], but whether the mechanism was an inhibition of lipolysis or a stimulation or re-esterification was not addressed.

Recently, several groups of investigators (Ahmed et al., 2010; Cai et al., 2008; Ge et al., 2008; Liu et al., 2009) have shown that, independent of pH or sodium ion, lactate inhibits lipolysis in fat cells through activation of an orphan G protein-coupled receptor (GPR81) (Figure 5). In mouse, rat, and human adipocytes, GPR81 appears to act as a lactate sensor with the inhibitory effect on lipolysis operating through cyclic-AMP (cAMP) and cAMP response element binding (CREB) (Bergersen, 2015; Hoque et al., 2014; Lauritzen et al., 2014).

Beyond a role in inhibiting lipolysis, lactate also plays an important role in limiting inflammation following injury. Consequently, lactate-containing solutions are being evaluated as anti-inflammatory resuscitation fluids for use in a variety of other therapies including acute pancreatitis (Hoque et al., 2014; Wu et al., 2011), hepatitis (Hoque et al., 2014), and dengue fever (Somasetia et al., 2014). Compared to normal saline, lactate-containing resuscitation solutions offer the advantage of providing calories as well as fluid and electrolytes. However, not until Hoque and colleagues (Hoque et al., 2014) found that lactate binding to GPR81 negatively regulates Toll-like receptor induction of the pyrin domain-containing protein 3 (NLRP3) inflammasome and production of IL-1β, via arrestin beta 2 (ARRB2) and GPR81, was the mechanism by which lactate suppressed inflammation in patients with acute organ injury understood.

In summary on this section, since the initial publication of Wu and colleagues (Wu et al., 2011), the anti-inflammatory effects of L-lactate therapy have been confirmed for several conditions including treatment of uterine inflammation during contractions (Madaan et al., 2017). Most recently, the work of de-Madaria et al. (2017) has been noteworthy because they identified the role of the L-lactate anion in Lactated Ringer's solution in the treatment of acute pancreatitis.

Lactate and Pyruvate as Inhibitors of Mitochondrial β-Oxidation

When glycolysis is accelerated during muscle contraction, lactate (L) and pyruvate (P) concentrations raise the lactate/pyruvate ratio, or L/P. At rest, the L/P in muscle and venous effluent from a muscle bed approximates 10, but the ratio rises more than an

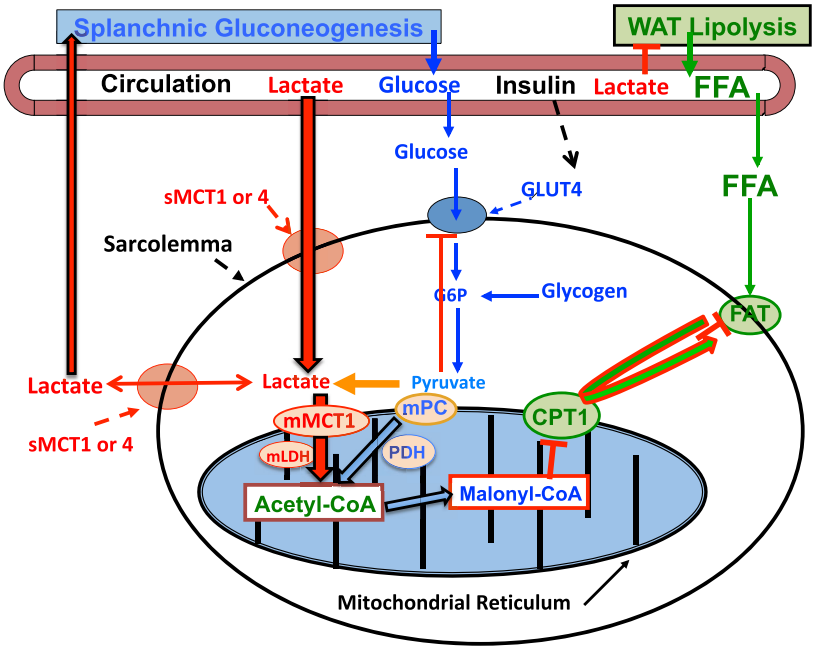

Figure 5. Central Role of Lactate Influencing Energy Substrate Partitioning

Illustration of how lactatemia affects blood [glucose] and peripheral glucose uptake as well as the production, uptake, and oxidation of FFA, giving rise to metabolic inflexibility in muscle. Lactate is the inevitable consequence of glycolysis (Rogatzki et al., 2015), the minimal muscle L/P being 10 and rising to an L/P > 100 when glycolytic flux is high (Henderson et al., 2007). Lactate is the favored oxidizable substrate and provides product inhibition of glucose and FFA oxidation. As the products of glycolysis, lactate and pyruvate provide negative feedback inhibition of glucose disposal (blue dashed lines). Also, as the predominant mitochondrial substrate, lactate gives rise to acetyl-CoA, and in turn malonyl-CoA. Acetyl-CoA inhibits β-ketothiolase and hence β-oxidation, while malonyl-CoA inhibits mitochondrial FFA-derivative uptake via CPT1 (**T**) (Saddik et al., 1993). Moreover, lactate is the main gluconeogenic precursor raising glucose production, raising blood [glucose] (red lines). Via GPR81 binding, lactate inhibits lipolysis in WAT (**T**), depressing circulating [FFA] (Hoque et al., 2014; Liu et al., 2009). This model explains the paradoxical presence of lactatemia in high-intensity exercise and insulin-resistant states with limited ability to oxidize fat (green lines). Modified from Hashimoto et al. (Hashimoto et al., 2008). CPT1, carnitine palmitoyl transporter-1; FFA, free fatty acid; FAT, fatty acid translocator comprised of CD36 and FABPc; GLUT, glucose transporter; s, sarcolemmal; m, mitochondrial; malonyl, CoA formed from exported TCA citrate controlled by the interactions of malonyl-CoA decarboxylase (MCD) and acetyl-CoA carboxylase (ACC); MCT, monocarboxylate transporter; mPC, mitochondrial pyruvate transporter; PDH, pyruvate dehydrogenase; WAT, white adipose tissue; (**T**), inhibition. Not shown is fatty acyl-CoA (FA-CoA) that will accumulate if FFAs are taken up by myocytes but blocked from mitochondrial entry by the effect of malonyl-CoA on CPT1. Accumulated intracellular FA-CoA will give rise to intramyocellular triglyceride (IMTG) and the formulation of LC-FA, DAG, and ceramides via inhibition of phosphatidylinositol 3-kinase (PI3K) and reducing GLUT4 translocation.

order of magnitude during moderate-intensity exercise (Henderson et al., 2004). By mass action the monocarboxylate pair floods into the mitochondrial reticulum (Brooks et al., 1999b; Passarella et al., 2008; Saddik et al., 1993), giving rise to acetyl-CoA and thereby malonyl-CoA formation (Figure 5). The rise in malonyl-CoA inhibits the entry of activated FFAs into the mitochondrial matrix by inhibiting carnitine-palmitoyl transferase-1 (CPT1) (McGarry et al., 1977; Saddik et al., 1993) (Figure 5). As well, the accumulation of acetyl-CoA could downregulate β-ketothiolase, the terminal and rate-limiting enzyme of the mitochondrial β-oxidation pathway.

Spermatogenic and Sertoli-Germ Cell Lactate Shuttles

The concept of spermatogenic lactate shuttles was introduced by L. Bruce Gladden in his classic review paper (Gladden, 2004). Gladden's review unified extant data in the literature and anticipated subsequent results in the field of fertility so important for human reproduction, veterinary medicine, and animal husbandry agriculture (Boussouar and Benahmed, 2004; Reynolds et al., 2017). Gladden's treatment of the subject has stood the test of time even as the technologies, including magnetic resonance spectroscopy (MRS), have become more sophisticated (Reynolds et al., 2017).

For decades it has been known that mammalian spermatozoa can use lactate as an aerobic energy source (Storey and Kayne, 1977). Noteworthy also is that in their seminal papers on discovery of MCT1 and MCT2, Garcia et al. noted high expression of MCT1 in sperm heads as they entered the epididymis, followed by lower expression of MCT1 expression as sperm coursed through the epididymis (Garcia et al. 1994, 1995). Earlier it was noted that lactate stimulates respiration in ejaculated bovine sperm (Halangk et al., 1985), and further, lactate maintains bovine sperm motility as well as glucose when sperm are studied or maintained *ex vivo* (Inskeep and Hammerstedt, 1985). More relevant to physiology is that just like fast twitch-glycolytic driver muscle fibers that fuel slow twitch-oxidative muscle fibers, Sertoli cells in testes secrete lactate, not glucose, to fuel sperm motility *in vivo*. In effect, then, the Sertoli-sperm cell relationship is the primal demonstration of cell-cell lactate shuttling. The Sertoli-sperm cell relationship is accompanied by an intracellular lactate shuttle *in vivo*. In fact, the subtitle to the 1977 paper by Storey and Kayne is "Direct intramitochondrial lactate oxidation by rabbit sperm mitochondria" (Storey and Kayne, 1977). In sperm, the mitochondrial reticulum is elaborate, large, and spiral shaped, located at the midpiece, at the base of the sperm head. In their ability to oxidize exogenously supplied lactate, the mitochondrial network is fueled as are mitochondria isolated from other tissues as described above (Baba and Sharma, 1971; Brandt et al., 1987; Brooks et al., 1999a; De Bari et al., 2004; Kline et al., 1986). And, just as in mitochondria isolated from other tissues, lactate is the preferred fuel for sperm mitochondria (Jones, 1997).

With regard to the presence of a mitochondrial lactate oxidation complex in the mitochondrial reticulum in sperm, existing data are supportive. For instance, with mitochondrial preparations from boar spermatozoa, external NADH was oxidized in the presence of external lactate, but this oxidation was inhibited by the MCT inhibitor α-cyano-4-hydroxycinnamate (Roth and Brooks, 1990a, 1990b) and by oxamate, an inhibitor of LDH

(Brooks et al., 1999c; Calvin and Tubbs, 1978). Noteworthy is that while oxamate blocks oxidation of lactate, pyruvate oxidation is, if anything, enhanced (Brandt et al., 1987). Thus as in mitochondrial preparations from other mammalian tissues (Brooks et al., 1999a; Butz et al., 2004), both MCT and LDH are required for the oxidation of lactate by sperm mitochondrial preparations. Those results on boar sperm mitochondria were supported by results on sperm mitochondria from rats and rabbits (Gallina et al., 1994). To be complete, it should be noted that although available data support the presence of a lactate shuttle in mitochondria from boars, rats, rabbits, and cattle, the lactate shuttle is not likely present in mouse spermatozoa (Gallina et al., 1994), and both lactate and malate-aspartate shuttles are present in spermatozoa of many species (Calvin and Tubbs, 1978), which is common in cells of many tissues from diverse mammalian species.

Lactate Shuttling in and out of the Gut Microbiome: A Gut-Soma Lactate Shuttle?

Functional roles for the gut microbiome and its role in health and disease are currently of significant interest (Turnbaugh et al., 2007), with preliminary data indicating relationships between microbiota and the prevalence of chronic diseases such as insulin resistance and metabolic syndrome (Vrieze et al., 2012). One of the underdeveloped areas of study concerns the role of lactate and other products of fermentation in promoting health of the gut mucosa. For example, inspired by findings on the role of lactate as a signaling molecule, investigators have observed lactate to downregulate pro-inflammatory responses in intestinal epithelial and myeloid cells (Iraporda et al., 2015). The same group has also observed anti-inflammatory effects of lactate in studies using a 2,4,6-trinitrobenzenesulfonic acid (TNBSP) model of induced colitis (Iraporda et al., 2016). Consequently, Iraporda and colleagues advocate for the consumption of lactate-containing foods for their favorable effects on the gut microbiota in general (Iraporda et al., 2014) and specifically for their potential role in protecting against intestinal pathogens such as *Salmonella* (Iraporda et al., 2017).

As was typical of other areas of investigation, to date, studies of gut lactate production and routes of disposal in the gut have been limited by the lack of flux (turnover) measurements. Lactate is a natural fermentation product, but little lactate appears in the feces (Flint et al., 2015). To some this might mean that lactate is unimportant for natural gut function, but an alternative view is apparent. This is that there is high turnover (appearance and disposal) of gut lactate. Lactate is a common end product of bacterial fermentation and is produced by many phyla of bacteria, in particular by lactic acid bacteria of the genera *Lactobacillus* and *Bifidobacterium*. Because of their purported health-promoting effects, these two genera are considered key members of the gut microbiota (Hill et al., 2014).

Lactate can appear in the gut via the consumption of probiotics such as fermented foods that, if eaten raw, contain live cultures of lactate-producing bacteria. Examples of fermented foods are kefir, yogurt, sauerkraut, pickles, miso, kimchi, and sourdough breads. In addition to consumption of fermented foods, lactate can appear in the gut as a dietary supplement, such as in a sports drink (Azevedo et al., 2007). Efficacy of providing lactate polymers and esters in in sports drinks and other dietary supplements is possible because rapid lactate uptake in the upper intestine is mediated by a sodium-lactate-mediated transporter (SMCT) (Coady et al., 2004; Teramae et al., 2010).

Lactate can also appear in the gut as the result of the consumption of prebiotic, fiber-containing foods that promote fermentation in the gut. Fibrous vegetables that function as prebiotics include asparagus, leeks, onions, grains, legumes, and cruciferous vegetables such as broccoli, brussels sprouts, cabbage, cauliflower, collard greens, kale, radish, and rutabaga. In the colon, *Lactobacillus*, *Bifidobacterium*, and Firmicutes ferment products of many fiber-containing carbohydrate foods to pyruvate and lactate. From there, lactate (2-hydroxy-propionate) is converted to propionate through the arcylate pathway by *Coprococcus catus* and *Megasphaera* species (Veillonellaceae). As well, lactate can be converted to acetate and butyrate by the CoA pathway through actions of several bacterial genera including *Eubacterium rectale* and *Coprococcus catus*. Alternatively, lactate can be converted to propionate by the succinate pathway by Bacteroidetes (*Veillonella* species *Dialister succinatiphilus* and *Phascolarctobacterium succinatutens*) bacteria. In terms of healthy gut function, butyrate, acetate, propionate, and succinate, but not lactate, are considered to be helpful substrates supporting metabolism in gut microbiota (Flint et al., 2015; Galland, 2014). But why has a potential role for lactate not been considered along with other monocarboxylates? Is historical, unconscious bias to be considered?

Production of lactate in the lower gut by *Lactobacillus* and *Bifidobacterium* and disposal via production and subsequent metabolism of butyrate, propionate, and succinate may be one reason why [lactate] is low in stool. Another, unstudied mechanism may be that of lactate release into systemic circulation via SMCTs (Coady et al., 2004; Teramae et al., 2010). Hints of gut lactate production within and release from the GI tract with disposal in other organs (i.e., a "gut-to-soma" lactate shuttle mechanism) may be found in the postprandial rise in blood L-lactate following CHO nutrition and presence of the indirect (glucose paradox) pathway (*vide supra*). Another clue is that in *ex vivo* studies of fermentation products from the action of gut microbiota on apple and beet fibers, 72-hr lactate accumulation was comparable to that of butyrate (Aguirre et al., 2014). And perhaps an even more profound hint supporting the presence of a gut-to-soma lactate shuttle may be that the gut releases D-lactate in feces (Galland, 2014). Because it is likely that gut microbiota produce a racemic (L- and D-lactic acid) mixture, and also because it is likely that the L-lactate enantiomer is metabolized in the gut and elsewhere, an accumulation of gut D-lactate is to be expected. However, accumulation of D-lactate could result in acidosis and irritation of the lower bowel. Further, release of D-Lactate into circulation could have neurotoxic effects (Chan et al., 1994; Galland, 2014; Thurn et al., 1985). Given the developing database on D-lactate formation and its toxic effects, it is not surprising that fecal transplantation has been tested as a treatment for D-lactic acidosis in a child with short bowel syndrome (Davidovics et al., 2016) and that "D-lactate free" probiotic products are being commercialized (e.g., http://organic3.com/supplements/probiotics/d-lactate-free-probiotics/).

To reiterate from above, it is likely that there is a very high turnover of L-lactate in the bowel that is not apparent using current

methods of investigation. However, considering the idea of simultaneous lactate production and utilization in the bowel, as well as some lactate release from the bowel into systemic circulation via SMCTs with disposal elsewhere in the body (i.e., a gut-soma lactate shuttle), interpretation of extant data is different from current ideas concerning the role of the microbiome in health and disease. Rather than the specific bacterial load itself, practices and mechanisms that promote the presence of gut lactate may be more important. For instance, the consumption of lactate-containing foods (Garrote et al., 2015) and gut fermentation that support gut lactate synthesis and accumulation can be important for gut health. Gut lactate not only supports integrity of gut mucosa, but also likely results in an intestinal environment that can sustain a number of different combinations of gut microbiota (Gilles, 2017).

An Organism-to-Organism Lactate Shuttle in Host-Pathogen Interactions?

Based on our research (Weilhammer et al., 2012), the question arose: can lactate shuttling occur across individuals and species as occur in host-pathogen interactions? *Toxoplasma gondii* is an obligate intracellular protozoan parasite of the phylum Apicomplexa. One of the most widespread parasites, *T. gondii* can infect a wide range of warm-blooded host species, including approximately one-third of the world's human population in both developed and developing countries (Tenter et al., 2000). The asexual life cycle of *T. gondii* within non-feline (intermediate) hosts involves conversion between two distinct forms: tachyzoites and bradyzoites. Tachyzoites are the fast-replicating form responsible for flu-like symptoms experienced during acute infection. During the course of infection, tachyzoites differentiate into bradyzoites, which are the slow-replicating form responsible for establishment of long-lived tissue cysts that persist during chronic infection. While tachyzoites can infect and replicate within virtually any nucleated cell, bradyzoite cysts are typically found within neural and muscle tissue (Weilhammer et al., 2012).

The sexual life of *T. gondii* occurs in cats that become infected from the ingestion of infected rodents and birds. Within intestines of infected cats, zygote-containing cysts are known as oocysts. When oocysts rupture, *T. gondii* is shed in cat feces. Although bradyzoite-containing tissue cysts can form in virtually any organ of intermediary hosts, tissue cysts predominantly form and persist in the brain, eyes, and striated muscle including the heart. Humans become infected from the consumption of inadequately cooked or cured meats of infected animals.

To evaluate the factors that regulate the stage conversion of parasites from tachyzoites into bradyzoites in host cells, Weilhammer et al. developed an *in vitro* system to evaluate resistance of different cell types to tachyzoite-bradyzoite conversion. By evaluating metabolic responses in infected host cells as well as media from infected cells, Weilhammer et al. (Weilhammer et al., 2012) identified that induction of glycolysis leading to lactate production was protective for conversion.

Their hypothesis was studied in several ways, including glucose incubation, identification of lactate as the protective component in incubation media, pharmacological blocking of glycolytic enzymes, and induction of glycolytic enzymes by upregulating expression of serine/threonine kinase protein kinase B (PKB), also known as Akt. Upregulating the expression of Akt was used as it is known to force induction of glycolytic enzymes and hence glycolysis in a variety of cell types. Akt activity is also physiologically relevant to *T. gondii* biology, as parasite infection induces host Akt activation and promotes parasite survival by inhibition of host cell apoptosis (Kim and Denkers, 2006).

As reviewed above, the transcription factor HIF-1α is induced by hypoxia as well as lactate and functions to upregulate glycolysis. *T. gondii* infection leads to the upregulation of host HIF-1α activity, and the induction of HIF-1α-dependent host genes appears to be required for parasite growth at physiological oxygen levels. Importantly, induction of host HIF-1α occurs via a cell-extrinsic mechanism where parasite secretion can induce HIF-1α activity in uninfected neighboring host cells (Spear et al., 2006; Weilhammer et al., 2012). Thus it appears that host cell glycolysis in uninfected cells can inhibit conversion in neighboring infected cells by the production and release of lactate.

Lactate Shuttles in Resuscitation and Treatment of Injuries and Illnesses

Given the ongoing revolution in understanding the role of lactate in metabolism, it is to be expected that some would undertake using new knowledge to improve outcomes in persons suffering injuries and illnesses (Brooks and Martin, 2015; Brooks and Mercier, 1994; Garcia-Alvarez et al., 2014; Marik, 2009). While elevated blood [lactate] (i.e., hyperlactatemia) is usual in exercise, particularly high-intensity exercise leading to high blood lactate levels, high-intensity exercise is increasingly recommended as a means to reduce risk factors of diabetes, coronary artery disease (CAD), and cardiometabolic disease (CMD) (Robinson et al., 2017). Hyperlactatemia is also typical of severe injuries such as the acute phase of TBI (Glenn et al., 2003), critical illnesses such as sepsis (Shapiro et al., 2005), and organ failure (Murphy et al., 2001). In clinical settings hyperlactatemia is a concern because it is a predictor of mortality (Shapiro et al., 2005; Zhang and Xu, 2014). Typically, the mechanism of lactatemia is assumed to be ischemia and hypoxemia. However, as reviewed by Garcia-Alvarez and colleagues, there is scant evidence for ischemia, hypoxemia, or tissue hypoxia when hyperlactatemia occurs in clinical conditions giving rise to hyperlactatemia (Garcia-Alvarez et al., 2014; Marik and Bellomo, 2013). Rather, the association between hyperlactatemia and severity of injury or illness is traceable to assumptions of O_2 debt theory, now approaching 100 years of age (Hill, 1924; Meyerhof, 1920), that are contrary to new ideas involving the lactate shuttle mechanism (Brooks, 1984, 2009). Therefore, the plea to instructors of biochemistry and clinicians is to understand lactate shuttling in mammalian biology as a strain response, the purpose of which is to mitigate the consequences of illness and injury; lactatemia is not the cause of injury or illness, but rather a mechanism to mitigate the effects of injury and illness. Despite adherence to O_2 debt theory by some, clinicians in several specialties in diverse global locations are investigating and finding successes with lactate therapy (Bouzat et al., 2014; Nalos et al., 2014; Sharma et al., 2005, 2008; Wolahan et al., 2017).

Although here we discuss numerous instances in which it may be clinically beneficial to achieve elevated blood lactate concentrations, a comment on the significance of lactate monitoring in illness when sepsis is suspected or feared is also important to consider. A blood lactate value of 4 mM is certainly a biomarker of severe sepsis (Shapiro et al., 2005; Zhang and Xu, 2014). But

what is the significance of a slightly elevated blood lactate concentration of 2.5 mM in a febrile patient when the normal blood lactate concentration range is 0.8–2.0 mM (Rivers et al., 2001)? Concern over the prospect of a blooming bacterial, viral, or fungal attack leading to sepsis needs to be appreciated from the context of the huge lactate clearance capacity in a healthy person (Miller et al., 2002b) and also that lactatemia is unlikely to be due to oxygen insufficiency (hypoxia) (Garcia-Alvarez et al., 2014; Marik and Bellomo, 2013, 2016). Anecdotally, the first experiments to use lactate clamp technology to study glucose-lactate interactions in healthy resting men put us, the investigators (Miller et al., 2002a, 2002b, 2005), onto a steep learning curve. From earlier work (Mazzeo et al., 1986; Searle and Cavalieri, 1972; Stanley et al., 1985) we knew the lactate production rate in a healthy resting person. So, using a hypertonic L-lactate solution, we gave lactate intravenously at the previously known Ra, expecting that a doubling of total lactate rate of appearance (endogenous plus exogenous) would raise blood [lactate]. But nothing happened to blood [lactate]. Consequently, we doubled and then tripled the exogenous L-lactate infusion rate before blood [lactate] rose significantly. So, even though in previous experiments we had calculated blood lactate metabolic clearance rate, we had no appreciation for the huge capacity of a healthy body to clear lactate. But to the point of recognizing the importance of a slight or moderate rise in blood [lactate] in a febrile patient, perhaps with elevated heart and breathing rates, a warning bell should sound. Specifically, is there some O_2-independent lactate generating infection somewhere that is either (1) starting to overwhelm the endogenous capacity for lactate clearance, (2) starting to limit the endogenous capacity for lactate clearance, or (3) an infection brewing that may give rise to overwhelming lactate production and/or compromise lactate clearance capacity? Alternatively, is the body readying for some challenge by raising the level of a key myocardial (Bergman et al., 2009) and whole-body energy substrate (Brooks, 2002), a gluconeogenic precursor (Bergman et al., 2000; Brooks, 1986; Emhoff et al., 2013b), or an anti-inflammatory moiety (Hoque et al., 2014; Wu et al., 2011)? Realizing the importance of lactate in supporting metabolism, some have proposed Lactated Ringer's solution as a resuscitation fluid in sepsis (Marik and Bellomo, 2016), and by extension of the same thinking, the use of isotonic or hypertonic sodium-L-lactate and Sanguisal (a contraction from Latin meaning blood [sanguis] and salt [sal], a physiologically balanced mixture of Na^+-, K^+-, Mg^{2+}-, and Ca^{2+}-lactate plus phosphate) also needs to be evaluated for resuscitation in sepsis.

Brain Injury

One major area of investigation in which lactate therapy is being applied experimentally and in clinical trials is the area of resuscitation following brain injury. In applying theory to practice, exogenous intravenous lactate infusion raising blood lactate concentration to levels of 4–5 mM, as seen in hard exercise (Messonnier et al., 2013), is being explored in the United States, Europe, and elsewhere. Despite initial hyperlactatemia as part of the immediate stress response to injury, in the days following injury inadequate nutrition, typically < 50% of need (Finfer et al., 2009), and glycogen depletion result in low circulating blood lactate levels after several days of hospitalization following severe TBI (Glenn et al., 2015a). Low arterial lactate concentration limits CHO uptake because injury results in a depression in cerebral glucose uptake (i.e., CMRGlucose) despite administration of glucose and CHO sources via enteral or parenteral feeding. Because cerebral lactate uptake is not limited following brain injury (Glenn et al., 2015b), the strategy of raising cerebral CHO uptake is to supply intravenous L-lactate, thus bypassing the injury-imposed limitation in CMRGlucose (Brooks and Martin, 2015).

Besides providing brain fuel following injury (Glenn et al., 2015b), L-lactate treatment is anti-inflammatory for two sets of reasons. First, if the vehicle of L-lactate delivery is intravenous Na^+-lactate, then raising plasma [Na^+] may lower intracerebral pressure (ICP) via an osmotic effect. And second and more importantly, the L-lactate (not D-) enantiomer (Boysen and Dorval, 2014; Chan et al., 1994; de-Madaria et al., 2017) is the effective ligand and binds to the putative lactate receptor GPR81 (Ahmed et al., 2010; Bergersen, 2015; Lauritzen et al., 2014) that, via cAMP and CREB, inhibits activation of inflammatory pathways (Hoque et al., 2014).

In terms of route of delivery, providing exogenous L-lactate via the i.v. mode of administration has advantages, especially when oral or gastric tube feeding is contraindicated by polytrauma or other complications. Depending on an individual's nutritive and physiological state, compared to that for glucose, lactate turnover can vary widely (Bergman et al., 1999a, 1999b; Messonnier et al., 2013; Stanley et al., 1988). Hence, rather than provide a L-lactate dose related to body mass, age, and gender, investigators set the lactate infusion dose to that which achieves a targeted (clamped) blood lactate concentration. In one study the L-lactate clamp (LC) was 2 mM (Wolahan et al., 2017). However, because the mass of lactate is essentially half that of glucose, other investigators have set LC targets to 4–5 mM (Bouzat et al., 2014; Patet et al., 2016; Quintard et al., 2016; Wolahan et al., 2017). Brain injury conditions to which LC treatments have been applied include TBI (Patet et al., 2016; Quintard et al., 2016; Wolahan et al., 2017) and subarachnoid hemorrhage (Oddo et al., 2012).

Heart Failure

During rest or exercise, lactate is a major fuel for the healthy heart; in fact, as a cardiac fuel, L-lactate is preferred over glucose and free fatty acids (Bergman et al., 2009; Gertz et al., 1981, 1988). Accordingly, it is not surprising that the treatment of heart failure is moving in the direction of providing exogenous lactate to improve cardiac function (Nalos et al., 2014; Sharma et al., 2008, 2005) (Figure 5).

Chronic, Obstructive Pulmonary Disease (COPD) and Heart Disease

Acute high altitude exposure results in lactatemia in resting individuals and greater blood lactate accumulation during given exercise power outputs compared with sea level (*vide supra*). Lactatemia at high altitude (i.e., the "lactate paradox") has been found to be due to activation of the sympathetic nervous system and not oxygen lack (*vide supra*) (Brooks et al., 1991a, 1991b). Lactatemia and hyperlactemia on easy exertion at sea level is characteristic of those with asthma and other forms of pulmonary disease (Casaburi et al., 1991) as well as heart disease and other conditions that limit pulmonary oxygen diffusion and systemic oxygen transport (Wasserman and McIlroy, 1964). Blood lactate and resulting ventilatory responses to graded

exercise (i.e., determining lactate and ventilatory "thresholds") are widely used paradigms in pulmonary and sports medicine, but interpretation of data is limited by the failure of clinicians to monitor parameters of lactate kinetics and responses of the sympathetic nervous system in response to hypoxemia (San-Millán and Brooks, 2018). Results exist only for graded (Messonnier et al., 2013) and continuous leg cycling exercise tests (Bergman et al., 1999b), and those results clearly indicate that the lactate threshold is attributable to an imbalance between the appearance of lactate in and disposal from blood. However, the meaning of blood lactate and ventilatory thresholds in activities such as running and swimming has not been studied and consequently is unknown.

Inflammation

Intravenous L-lactate infusion has the capability of minimizing cerebral swelling and ICP following brain injury, but vascular L-lactate infusion has the potential to minimize inflammation in other injured tissues as well. Notably, L-lactate therapy is attracting attention and consideration for use in a variety of other therapies, including pancreatitis (Hoque et al., 2014; Wu et al., 2011), hepatitis (Hoque et al., 2014), dengue fever (Somasetia et al., 2014), and sepsis (Marik and Bellomo, 2016).

When Lactate Shuttling May Be Maladaptive

Until now in this review, normal physiological functioning of lactate shuttles has been emphasized; however, there are cases in which lactate shuttling can be problematic or pathological. For instance, in cancer, aggressiveness of the disease is associated with the extent of hyperlactatemia (Hanahan and Weinberg, 2011). There is a long history of interest in lactate production and accumulation in cancer research (the "Warburg effect"), and recently investigators have sought to block lactate shuttling in tumors by blocking MCTs (Sonveaux et al., 2008). Recently also, in the field of diabetes, research investigators have sought to understand why MCT expression is silenced in pancreatic β cells such that they do not participate in lactate shuttling (Ishihara et al., 1999; Otonkoski et al., 2007). Silencing of MCT1 expression and insertion into the plasma membrane is necessary to prevent hypersecretion of insulin and profound hypoglycemia when blood lactate is high and blood glucose is low, as occurs in physical exercise.

Lactate Shuttles in Cancer Metabolism

In 1923 Otto Warburg observed the first phenotypic characteristics of cancer cells; they demonstrated increased glucose uptake and excessive lactate formation even under fully oxygenated conditions (Warburg and Minami, 1923). Warburg's discovery was subsequently named the "Warburg effect" (Racker, 1972). The high glucose uptake/lactate release phenotype remains a hallmark of cancer (Hanahan and Weinberg, 2000; Koppenol et al., 2011), but today there is no consensus on the meaning of the observations. It was the excessive lactate formation that struck Warburg and led him to propose that cancer was an injury to the cellular respiratory apparatus. In a recent review, San-Millán and I (San-Millán and Brooks, 2017) described many similarities between cancer and healthy exercise phenotypes. Consequently, we proposed that augmented lactate production ("lactagenesis") initiated by gene mutations is the reason and purpose of the Warburg effect and that dysregulated lactate metabolism and signaling are key elements in carcinogenesis (San-Millán and Brooks, 2017). In this regard it is to be noted that we are not the only physiologists to have commented on the meaning of the Warburg effect in an age when there is growing understanding of lactate shuttling (Goodwin et al., 2015). An abbreviated justification of our hypothesis (San-Millán and Brooks, 2017) is given below.

Lactate Production in Carcinogenesis

In lactagenic cancers, oncogenes and mutated tumor suppressor factors behave with the apparent purpose of reprogramming glycolysis for lactagenesis, thus creating concentration gradients for lactate exchange within, between, and among cells. We (San-Millán and Brooks, 2017) identified the following steps by which lactagenesis may support carcinogenesis: (1) increased glucose uptake; (2) increased glycolytic enzyme expression and activity; (3) decreased mitochondrial function; (4) increased lactate production, accumulation, and release; and (5) upregulation of monocarboxylate transporters MCT1 and MCT4 for lactate exchange. Not only is lactate present as the result of aberrant, inefficient metabolism, but because of its autocrine-, paracrine-, and endocrine-like characteristics we postulate that lactate participates in driving main sequela for carcinogenesis, specifically angiogenesis, immune escape, cell migration, metastasis, and self-sufficient metabolism. Accordingly, developing therapies that limit lactate exchange and signaling within and among cancer cells should be priorities for cancer research (San-Millán and Brooks, 2017).

Lactate Promotes Angiogenesis

It is well known that lactate is a key player in angiogenesis because it (lactate) stimulates release of vascular endothelial growth factor (VEGF) for wound healing and repair (Hunt et al., 2008; Kumar et al., 2007; Trabold et al., 2003). In cancer, lactate stimulates VEGF protein expression in endothelial cells (Dhup et al., 2012; Polet and Feron, 2013; Végran et al., 2011) in a concentration-dependent manner (Beckert et al., 2006). When lactate production is blocked using oxamate, a LDHA inhibitor, angiogenesis is greatly reduced (Hunt et al., 2008). Related is that LDH knockout inhibits cancer cell proliferation (Fantin et al., 2006; Shim et al., 1997), while approaches to target MCTs, thereby blocking lactate transport across cancer cell membranes, have shown effectiveness in decreasing both angiogenesis and cell migration (Doherty et al., 2014; Draoui and Feron, 2011; Sonveaux et al., 2012).

Lactate Influences Acidity of the Tumor Microenvironment (TME)

The TME is an active niche that shapes tumor pathogenesis and evolution (Chen et al., 2015). The TME consists of malignant cells, immune cells, non-cancer cell stromas, fibroblasts, and the vasculature and lymphatics. Because MCTs are symporters, cotransporting lactate anions and protons, the intracellular pH (pHi) in cancer cells tends to be slightly alkaline compared to the extracellular space into which protons are excreted (Gillies et al., 2002; Stubbs et al., 2000). In normal cells, pHi approximates 7.2. However, in cancer cells pHi approximates 7.4 (Webb et al., 2011), or the pH of normal arterial blood. In contrast, an extracellular pH of 5.5–7.0 is common in cancers (Justus et al., 2013; Webb et al., 2011). As the result of constant lactate and hydrogen ion extrusion from cancer cells by ontogenetic-derived MCT overexpression, the TME becomes an acidic environment, which seems to be key for carcinogenesis (Gillies et al.,

2002; Stubbs et al., 2000). In fact, TMEs with the lowest pH correlate with the highest level of invasion and vice versa (Corbet and Feron, 2017).

Lactate Promotes Cell Migration, Metastasis, and Exosome Release

Cell migration is an essential step in carcinogenesis and metastasis. Among other factors, lactate appears to be necessary for endothelial cell migration (Beckert et al., 2006; Walenta and Mueller-Klieser, 2004) in a concentration-related manner (Goetze et al., 2011). Further, in glioma cells, lactate induces the expression of transforming growth factor-β2 (TGF-β2), a key regulator of glioma cell migration (Baumann et al., 2009). A role for lactate in stimulating metastasis has long been suspected because of the correlation between lactate level and the extent of metastasis in different forms of cancers (Brizel et al., 2001; Dhup et al., 2012; Schwickert et al., 1995; Walenta and Mueller-Klieser, 2004).

Exosomes are considered by some to represent another mechanism for tumor metastasis. Exosomes are microvesicles, 30–100 nm in size, of endocytic origin that contain microRNAs, proteins, metabolic enzymes, and structural proteins representative of the cells from which they originate. Secreted cancer-derived exosomes can be transferred to stroma cells in the cancer microenvironment and may induce epigenetic changes and elicit cancer phenotype in target cells by transferring genetic information including oncogenes and onco-miRNAs (Kharaziha et al., 2012). Cancer-associated fibroblast exosomes provoke metabolic reprograming in other cancer cells by inhibiting mitochondrial function and upregulating glucose metabolism (Zhao et al., 2016). In cancer patients tumor-derived exosome release correlates with poor prognosis (Kim et al., 2003). An important regulator of exosome release by tumors is low pH in the tumor microenvironment, caused by the release of protons and lactate anions from within rapidly glycolyzing cancer cells (Parolini et al., 2009). Treatment with proton pump inhibitors results in a marked inhibition of exosome release by tumor cells (Federici et al., 2014) and inhibition of exosome trafficking in tumors (Parolini et al., 2009). Because low pH can also be crucial in exosome release and uptake, blocking MCT expression or action in the TME might be a viable way of limiting lactate shuttling within a tumor.

Lactate Plays a Role in "Immune Escape"

Lactate appears to contribute to the immune escape by effects on monocytes, T cells, and natural killer (NK) cells. Monocytes are highly motile cells and precursors of tumor-associated macrophages. Lactate inhibits monocyte migration and the release of cytokines TNF and IL-6 (Goetze et al., 2011). As well, lactate appears to have a bimodal effect on T cell activation. On one hand, T cell activation increases glycolysis and lactate accumulation due to low cellular mitochondrial content (Michalek and Rathmell, 2010), but on the other hand, lactate accumulation in the TME opposes T cell lactate efflux, leading to decreased cytokine production and cytotoxic activity of human T cells (Fischer et al., 2007). This conclusion about the effect of lactate accumulation on T cells in the TME (San-Millán and Brooks, 2017) is supported by a recent report that tumor-derived lactate accumulation translationally inhibits expression of adhesion kinase family-interacting protein of 200 kD (FIP200) by downregulating NAD^+ cytosol level while upregulating the inhibitory effect of adenylate-uridylate-rich elements within the 3′ untranslated region of *Fip200* mRNA (Xia et al., 2017). Further, lactate inhibits the differentiation of monocytes to dendritic cells (Gottfried et al., 2006; Puig-Kröger et al., 2003). And finally, lactate in the TME inhibits NK cell function directly by inhibiting cytolytic function and indirectly by increasing the numbers of myeloid-derived suppressor cells that inhibit NK cytotoxicity (Husain et al., 2013). Hence, via lactate production and accumulation, the Warburg effect may contribute to immune escape in carcinogenesis.

Lactate Is Necessary for Cancer Cell Self-Sufficiency and Sustained Glycolysis

Both directly, as an energy source, and indirectly, as a gluconeogenic precursor, lactate plays a central role in the bioenergetics and self-sufficiency of cancer cells. Chronic sustained high rates of glycolysis in cancer cells will eventually deplete their own and then the body's glucose and glycogen reserves necessary to sustain high rates of glucose uptake in cancer cells. Subsequently, with glucose and glycogen depletion in the host patient, counter-regulatory mechanisms to maintain euglycemia will result in catabolism of body tissue protein reserves.

Carbon recycling in the Cori cycle arm of lactate shuttling is typically portrayed as a means to preserve euglycemia in a person, but effectiveness of the cycle is short-term and imperfect because both the precursor and products of glycolysis (glucose and lactate, respectively) are oxidized and thus depleted during functioning of the cycle. Consequently, as in other instances such as prolonged exercise and lack of CHO nutrition, body corpus amino acid and protein reserves are called upon to ensure long-term maintenance of euglycemia in the host.

Cachexia in cancer stresses the total body nitrogen pool as well as reserves of particular amino acids, particularly glutamine, as glutaminolysis is upregulated in many types of cancers (Daye and Wellen, 2012; Medina, 2001). Glutamine is converted to glutamate by glutaminase (GLS) that is overexpressed in cancers and regulated by c-MYC (Wise et al., 2008). Subsequent to conversion to glutamate, the carbon skeleton originating from glutamine is a readily available oxidative substrate via entry into the mitochondrial TCA cycle.

Beyond serving as an energy substrate via conversion to glutamate, in cancer, glutaminolysis also produces lactate. The pathway involves oxidation of glutamine to malate and then to pyruvate by malic enzyme (ME), which is overexpressed in different cancers and regulated by p53 (Jiang et al., 2013). Following conversion to pyruvate by the action of LDHA, which is overexpressed in lactagenic cancers (Brand et al., 2016; Shim et al., 1997), glutaminolysis leads to an increase in lactate production (San-Millán and Brooks, 2017). Further, in oxidative cancer cells, lactate promotes glutamate uptake and catabolism by increasing the expression of glutamine transporter ASCT2 and of glutaminase 1 (GLS1) (Pérez-Escuredo et al., 2016). Thus, in cancer, glutaminolysis can be regarded as a secondary carbon source for lactagenesis; by direct and indirect mechanisms, glutaminolysis both fuels cancer cells and depletes the host's body of CHO, amino acids, and protein reserves.

Lactate as a Transcription Factor

Exercise, including vigorous exercise leading to lactatemia, reduces cancer risk (Gohil and Brooks, 2012; Lee et al., 2012; Ruiz-Casado et al., 2017), but because of classic findings around the Warburg effect involving augmented glucose uptake and lactate production, concern persists over whether high-intensity

exercise involving increased glucose and lactate flux rates might provoke carcinogenesis or recurrence of cancer (Toohey et al., 2016). Rephrased, there is concern that lactatemia from high-intensity exercise could be a gene regulator contributing to metabolic reprogramming and development of the "cancer phenotype." We have shown that exposure to 10–20 mM of lactate upregulated 673 genes in non-transformed L6 cells (Hashimoto et al., 2007). Further, with MCF7 cells incubated in 10 mM lactate, a concentration observed in many cancer cells, ~4,131 genes were upregulated (Martinez-Outschoorn et al., 2011). Lactate increases MCT1 expression that is enhanced by c-Myc and p53. Further, the master transcription factor involved in tumor cell glycolysis, HIF-1, has been shown to be activated by lactate in different cancer lines (De Saedeleer et al., 2012; Lu et al., 2002; Semenza, 2010). Hence, it is plausible to think that the thousands of genes upregulated by lactate may collectively represent a transcriptional network involved in reprogramming cells for lactagenesis and perhaps carcinogenesis.

Blocking Lactate Shuttles in Cancer

Since Sonveaux et al. in the Feron lab identified lactate shuttling in tumors (Sonveaux et al., 2008), there have been serious attempts to repress tumorigenesis by blocking the release of lactate from glucose-consuming and highly glycolytic cells and cells respiring lactate. That cancer cells respire with lactate drawn from the TME is an important realization in itself (Hensley et al., 2016; Hussien and Brooks, 2011), but also oxidative lactate disposal within tumors sets up the concentration gradient necessary for lactate shuttling. Following the lead of Sonveaux et al. (Sonveaux et al., 2008), the search is on to develop MCT1 and MCT4 inhibitors (Doherty and Cleveland, 2013; Doherty et al., 2014; Draoui and Feron, 2011; Draoui et al., 2014; Sonveaux et al., 2008). However, lack of MCT specificity has been a problem. Recently, AstraZeneca developed a specific MCT1 and MCT2 inhibitor, AR-C155858 (Ovens et al., 2010), inhibiting MCT1 and MCT2 expression in Ras-transformed fibroblasts. However, the cells developed resistance to the inhibition of MCT1 and MCT2 and increased carcinogenesis by overexpressing MCT4 (Le Floch et al., 2011). New generations of MCT-1 inhibitors have shown promising results in Raji cells (Doherty et al., 2014) and small-cell lung cancer (Polański et al., 2014). However, the quest to find cancer-specific MCT blockers has as yet been unsuccessful; hence, others are looking for alternative approaches to blocking lactate shuttling in tumors and cancer, such as by limiting expression of CD147, the scaffold for MCT insertion into cell membranes (Baba et al., 2008; Schneiderhan et al., 2009; Su et al., 2009; Zou et al., 2007).

Lack of MCT Pancreatic β-Cell MCT Silencing Can Interfere in the Regulation of Glycemia

Lactate-glucose interactions can be complex, and by interfering with glucose-insulin signaling, lactate shuttling can be disruptive. Glucose and glycogen are the precursors to lactate formation (Brooks, 2002; Hultman, 1967), and lactate is the major gluconeogenic precursor (Bergman et al., 2000; Cori and Cori, 1946; Emhoff et al., 2013b; Meyer et al., 2002a, 2002b). However, whereas blood glucose level plays an important role in the regulation of its clearance rate via influencing the levels of insulin and counter-regulatory hormones, other than providing precursor material for gluconeogenesis, lactate is excluded from processes related to insulin secretion.

MCTs are ubiquitous, expressed in most tissues (Brooks, 2009; Garcia et al., 1994; Price et al., 1998), where they support lactate shuttling. The importance of lactate in metabolic regulation is further emphasized by exclusion of MCTs from insertion into pancreatic β cell plasma membranes (Pullen et al., 2010; Rutter et al., 2015). There, MCT expression is silenced to keep extracellular lactate from affecting intracellular redox and interfering with glucose sensing and insulin secretion (Bender et al., 2006). The silencing of MCT1 in pancreatic β cells is evolutionary proof of how lactate overrides glucose in regulating energy substrate partitioning in general and insulin secretion in particular when the dominant role of lactate must be suppressed. Noteworthy in this regard is that individuals experiencing failed suppression of pancreatic β cell MCT expression become hypoglycemic during hard exercise, leading to lactatemia as lactate gains entry to pancreatic β cells and affects cell redox as if blood glucose was elevated. In these individuals, unlike in healthy controls, aberrant entry of lactate into pancreatic β cells causes insulin secretion during exercise. The combination of high insulin and increased glucose disposal through metabolism causes hypoglycemia (Otonkoski et al., 2007).

What Can Be Learned by Distinguishing between the Terms "Aerobic Glycolysis" and "Fermentation" in Understanding Lactate Metabolism?

As assessed from recent literature, more and more diverse sets of investigators are finding support for the lactate shuttle hypothesis. In some aspects, confirmation of the hypothesis is helpful in terms of science. As well, confirmation is necessary because of the intellectual and organizational silos we live and work in; hence the lactate shuttle, a theory of metabolic organization developed in exercise physiology and metabolism, needed to be tested by investigators in neuroscience and cancer research who will accept results of their own investigations. For instance, using isotope tracer technology on mice, investigators (Hui et al., 2017) recently stated that "intravenous infusions of ^{13}C-labeled nutrients reveal that, on a molar basis, the circulatory turnover flux of lactate is the highest of all metabolites and exceeds that of glucose by 1.1-fold in fed mice, and 2.5-fold in fasting mice." The same authors concluded that "analysis reveals that during the fasted state, the contribution of glucose to tissue TCA metabolism is primarily indirect (via circulating lactate) in all tissues except the brain." However, all of this had been shown previously on mammalian models (Depocas et al., 1969; Freminet et al., 1974) and humans (Bergman et al., 2009; Brooks et al., 1991a; Messonnier et al., 2013; Miller et al., 2002a, 2002b; Stanley et al., 1988). Further, the statement about brain lactate metabolism by Hui et al. (Hui et al., 2017) is imprecise because it has been shown that lactate is preferred over glucose when arterial [lactate] is raised by physical exercise (Hashimoto et al., 2018; van Hall et al., 2009) or exogenous infusion (Brooks and Martin, 2015; Glenn et al., 2015b; Wolahan et al., 2017) (Figure 5).

With regard to recent replication of previous results, other investigators (Chen et al., 2016) used solid-state NMR, high-resolution mass spectrometry (HRMS), and transmission electron microscopy (TEM) on isolated cells *in vitro* to confirm important aspects of lactate shuttling and mitochondrial lactate oxidation. ^{13}C-NMR spectral analysis showed mitochondrial

lactate oxidation in cultured HeLa cells *in vitro*; the results help generalize previous results obtained by MRS on rat muscle in the Tom Jue lab (Park et al., 2015); on lactate oxidation in mitochondria isolated from rat muscle, heart, and liver (Brooks et al., 1999a; Kline et al., 1986); and on human skeletal muscle (Jacobs et al., 2013). Also, the authors (Chen et al., 2016) did well using TEM to show the presence of LDH in mitochondria of HeLa cells, but again, the presence of mitochondrial LDH has previously been shown in mammalian (Baba and Sharma, 1971; Brooks et al., 1999c) including human tissues (Dubouchaud et al., 2000) using EM. As well, mitochondrial LDH has been previously demonstrated by other methods, such as differential centrifugation followed by immunocoprecipitation and immunocytochemistry, on muscle-derived cell lines and rat (Hashimoto et al., 2006, 2005) and human muscles (Dubouchaud et al., 2000) as well as rat brain *in vivo* (Hashimoto et al., 2008).

In science, replication is important, but even so, from my perspective it is genuinely puzzling why so many contemporary investigators struggle to comprehend lactate shuttle theory. Perhaps comprehension is low due to reliance on outdated and inappropriate textbook terminology. Consider, for instance, interpretation of data by authors who studied a variety of cell types and intact mice under fully aerobic conditions (Chen et al., 2016; Hui et al., 2017). The investigators could not escape from thinking of and presenting their ideas in terms of "fermentation." An example of how loose usage of terminology leads to misunderstanding is illustrated by this (incorrect) Wikipedia entry: "Fermentation is a metabolic process that consumes sugar in the absence of oxygen. The products are organic acids, gases, or alcohol. It [fermentation] occurs in yeast and bacteria and also in oxygen-starved muscle cells, as in the case of lactic acid fermentation" (https://en.wikipedia.org/wiki/Fermentation). In human physiology, use of the term "fermentation" is appropriate when describing metabolism of gut microbiota (*vide supra*). And while bacteria in the microbiome are on us and in our gut, use of such terminology for understanding mammalian or human intermediary metabolism is unfortunate because the Wiki definition is not correct for intermediary metabolism in cells, organs, and tissues of mammals and humans. Further, the Wiki definition is lacking for understanding of human intermediary metabolism because there is no distinction between the metabolism of L- and D-lactate enantiomers. Hence, the concept of fermentation in guiding mammalian metabolism needs to be discarded because it ignores the fact that lactate production occurs continuously under fully aerobic conditions in humans and other mammals *in vivo*. And, of course, alcohol production is not a feature of glycolysis in human or mammalian metabolism.

The importance of proper terminology in describing glycolysis in mammalian and human systems has long been a feature of discussion in human physiology (Brooks and Fahey, 1984; Connett et al., 1990). However, with the advent of interest in the microbiome, physiologists, biochemists, and nutritionists focusing on the human condition need to become aware that fermentation takes place in the gut and the products include D- as well as L-lactate (*vide supra*).

Synopsis

Studies on mammals, including humans, during rest and exercise led to discovery of the lactate shuttle, a mechanism by which lactate production in rapidly glycolyzing cells provides energy substrate for recipient cells where lactate is a fuel energy source, gluconeogenic precursor, and signaling molecule. In heart and red skeletal muscle, lactate disposal is by mitochondrial respiration. In the liver and kidneys, mitochondria play roles in oxidizing lactate to pyruvate and then in the conversion to oxaloacetate and phosphoenolpyruvate via pyruvate carboxylase and phosphoenolpyruvate carboxykinase. As well, in the liver and kidneys, the oxidation of lactate and other fuel sources provides energy for completion of gluconeogenesis and glycogen synthesis. By changes in cell redox owing to the production and oxidation of lactate, as well as allosteric binding to GPR81, lactate affects numerous processes. Discoveries of many intracellular, cell-cell, and organ-organ lactate exchanges has led to articulation of numerous "lactate shuttles," the basis of which are interactive effects between producer and consumer cells.

It is anticipated that when clinicians better understand that glycolysis leading to lactate production is part of normal, aerobic physiology, they will be better able to treat the ill and injured. For example, exogenous L-lactate vascular infusion is being evaluated in the treatment of heart failure (Nalos et al., 2014; Sharma et al., 2008, 2005), TBI (Brooks and Martin, 2015; Oddo et al., 2012; Patet et al., 2016; Wolahan et al., 2017), pancreatitis (Hoque et al., 2014; Wu et al., 2011), hepatitis (Hoque et al., 2014), dengue fever (Somasetia et al., 2014), and sepsis (Marik and Bellomo, 2016).

Recognizing also that rising lactate level is a biomarker for an imbalance in lactate Ra and Rd, in diverse fields clinicians are paying increasing attention to the meaning of a rise in blood [lactate]. Those fields range from exercise physiology and sports medicine (Hofmann and Pokan, 2010; San-Millán and Brooks, 2018) to critical care medicine (Marik and Bellomo, 2013) and oncology (Sonveaux et al., 2008). Indeed, recognition that lactate shuttles among producer (driver) and consumer (recipient) cells in tumors offers the exciting possibility of reducing carcinogenesis and tumor size by blocking producer and recipient arms of lactate shuttles within and among tumor cells. As well, with appreciation of the importance and extent of lactate shuttling *in vivo*, it is to be anticipated that by controlling blood [lactate] via a closed-loop continuous monitoring system involving infusion of more or less lactate-containing, gluconeogenic, or monocarboxylate-containing solutions, the standard of care for treatment of the ill, injured, and malnourished will be improved (Horning and Brooks, 2012a, 2012b, 2015).

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DECLARATION OF INTERESTS

G.A.B. holds the following patents: US5420107 (Method and composition for energy source supplementation during exercise and recovery), US6482853 (Lactate thiolester for cardiac energy resuscitation and prevention of reperfusion injury and use as an energy supplement during exercise and recovery), US67438821 (Glycerol-lactate ester for use as an energy supplement during exercise and recovery), US8927490B2 (Systems and methods to estimate nutritional needs of human and other patients), US9232815 (Blood lactate range targets and nutritional formulations and protocols to support patients),

US9557334B2 (Formulations and methods to provide nutrition to human and other patients), and US9687011B2 (Blood lactate range targets and nutritional formulations and protocols to support patients).

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