Muscle as a consumer of lactate

L. BRUCE GLADDEN

Department of Health & Human Performance, Auburn University, Auburn, AL 36849-5323

ABSTRACT

GLADDEN, L. B., Muscle as a consumer of lactate. *Med. Sci. Sports Exerc.*, Vol. 32, No. 4, pp. 764–771, 2000. Historically, muscle has been viewed primarily as a producer of lactate but is now considered also to be a primary consumer of lactate. Among the most important factors that regulate net lactate uptake and consumption are metabolic rate, blood flow, lactate concentration ([La]), hydrogen ion concentration ($[H^+]$), fiber type, and exercise training. Muscles probably consume more lactate during steady state exercise or contractions because of increased lactate oxidation since enhancements in lactate transport due to acute activity are small. For optimal lactate consumption, blood flow should be adequate to maintain ideal [La] and $[H^+]$ gradients from outside to inside muscles. However, it is not clear that greater than normal blood flow will enhance lactate exchange. A widening of the [La] gradient from outside to inside muscle cells along with an increase in muscle [La] enhances both lactate utilization and sarcolemmal lactate transport. Similarly, a significant outside to inside $[H^+]$ gradient will stimulate sarcolemmal lactate influx, whereas an increased intramuscular $[H^+]$ may stimulate exogenous lactate utilization by inhibiting endogenous lactate production. Oxidative muscle fibers are metabolically suited for lactate oxidation, and they have a greater capacity for sarcolemmal lactate transport than do glycolytic muscle fibers. Endurance training improves muscle capacity for lactate utilization and increases membrane transport of lactate probably via an increase in Type I monocarboxylate transport protein (MCT1) and perhaps other MCT isoforms as well. The future challenge is to understand the regulatory roles of both lactate metabolism and membrane transport of lactate. **Key Words:** EXERCISE, LACTATE METABOLISM, LACTATE TRANSPORT, MONOCARBOXYLATE TRANSPORT, MUSCLE METABOLISM

At rest, muscles slowly release lactate into the blood on a net basis, although at times they may show a small net uptake. During exercise, particularly short-term high-intensity exercise, muscles produce lactate rapidly, whereas lactate clearance is slowed. This results in an increased intramuscular lactate concentration ([La]) and an increased net output of lactate from the muscles into the blood. Later, during recovery from short-term exercise, or even during continued, prolonged exercise, there is net lactate uptake from the blood by resting muscles or by other muscles that are doing mild to moderate exercise. During prolonged exercise of low to moderate intensity, the muscles that originally showed net lactate output at the onset of the exercise may actually reverse to net lactate uptake (33). This shuttling of lactate (14–18) between adjacent muscles and between muscles and blood raises intriguing questions concerning how and why lactate is produced or consumed by skeletal muscles. The present paper will discuss factors that might regulate lactate consumption by muscle. A partial list of the most important factors studied to date includes: metabolic rate, blood flow, [La], hydrogen ion concentration ($[H^+]$), fiber type, and exercise training.

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METABOLIC RATE

Effects on lactate metabolism. Typically, an elevated metabolic rate is associated with a faster glycolytic rate and concomitant lactate production. However, if the metabolic rate is elevated without a large increment in glycolysis, then net lactate utilization could be increased due to a faster rate of pyruvate and NADH oxidation. These requirements are likely met during steady-state submaximal exercise. Net lactate utilization may also be increased during more intense exercise after the contracting muscles have gone through an initial transient period (first 10–15 min) of rapid lactate release (19,31,33,75). Numerous studies of blood [La] decline during exercising recovery (e.g., 22,44,65) support the notion that an increase in muscle metabolic rate stimulates net muscle lactate uptake as do studies of isotopically labeled lactate during exercise in intact animals and across contracting muscle groups (15–17).

Gladden et al. (32,35) have directly addressed the role of metabolic rate in net lactate uptake by the canine gastrocnemius *in situ*. Lactate/lactic acid was infused to elevate arterial plasma [La] while maintaining normal acid-base status. As illustrated in Figure 1, net lactate uptake was greater (with an elevated arterial [La] of ≈9 mM) during 4-Hz twitch contractions (high metabolic rate) in comparison with 1-Hz twitch contractions (moderate metabolic rate) or rest (low metabolic rate). Because the net lactate uptake measurements were done under steady-state conditions, they imply that the increased uptake represents an increased utilization of lactate. An interesting point of this study (32) is that, after an initial transient period, there was substantial

net lactate uptake by a muscle contracting at greater than 90% of $\dot{V}O_{2peak}$ for twitches. Similar experiments have not been done during tetanic contractions. This could be of considerable interest because $\dot{V}O_{2peak}$ for the dog gastrocnemius during tetanic contractions is greater than 240 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in comparison to only 140 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ for twitch contractions (51).

Effects on lactate transport. Before the muscle can metabolize lactate from an external source, the lactate must cross the sarcolemmal membrane. Clearly, glucose transport in skeletal muscle is turned on by exercise (30,38,41,64,81). Does exercise similarly activate lactate transport?

Only a few studies (9,62,85) have evaluated the impact of acute exercise or contractions on sarcolemmal lactate transport. Overall, this evidence suggests that any enhancement of lactate transport by exercise is minimal (≈0–28%) when compared with the increases that are typically reported for muscle glucose uptake (≈62–400%) in response to exercise (30,38,64,81). Acute lactate transport responses also appear to be minor in comparison with the increases in lactate production, utilization, and flux that are engendered by muscle contractions. This implies that an increase in lactate transport is not an important, acute regulatory response to exercise (33,48). Instead, it appears that increased transmembrane lactate flux during exercise is more likely due to increased transmembrane [La] and [H^+] gradients (8). However, some reservation is warranted given that lactate transport *during* contractions has not been satisfactorily assessed due to experimental limitations.

BLOOD FLOW

Both Juel (48) and Gladden (31) have discussed circumstantial evidence which suggests that lactate exchange, including uptake, might be enhanced by higher muscle blood flow. Most of this evidence is correlational in nature, such as Jorfeldt's report (45) that the rate of lactate uptake by human forearm muscle during lactate infusion related more closely to the product of arterial [La] and muscle blood flow than with arterial [La] alone. There have been only a couple of studies that have attempted to directly evaluate the potential role of blood flow on lactate exchange (34,85).

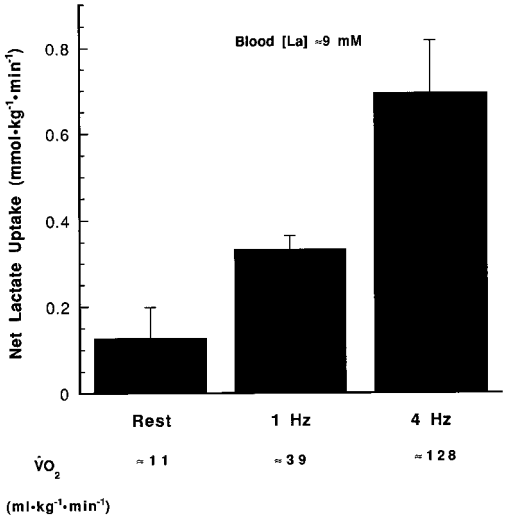

Figure 1—Net lactate uptake during rest and steady state contractions at 1 twitch per second (1 Hz) and 4 twitches per second (4 Hz) in the surgically isolated canine gastrocnemius muscle *in situ* with arterial blood [La] elevated by infusion of lactate. Note the differences in metabolic rate ($\dot{V}O_2$) among the three steady state conditions. [Redrawn with permission from data of Gladden, L. B. Net lactate uptake during progressive steady-level contractions in canine skeletal muscle. *J. Appl. Physiol.* 71:514–520, 1991 (32).]

In one of these studies, Gladden et al. (34) investigated the effect of blood flow on net lactate uptake in the dog gastrocnemius *in situ*. In all trials, metabolic rate (1-Hz twitch contractions) and blood [La] (≈12 mM) were elevated and held constant while blood flow was varied. An increase in blood flow to ≈165% of the normal spontaneous level had no significant effect on net lactate uptake, whereas net lactate uptake was increased by 29% when the blood flow was further increased to ≈200% of normal. Altogether, these experiments suggest a minor role for blood flow in determining net lactate uptake in this preparation. It remains uncertain, however, whether or not these results extend to the much higher metabolic rates that are possible in tetanic contractions with a more favorable duty cycle (12,13,23,51) or to asynchronous contractions during exercise *in vivo*. Furthermore, the potential effect of flow heterogeneity on lactate exchange has not been evaluated. The critical factor would be net lactate uptake/perfusion (L/Q) matching (31).

Possible effects of flow on the transport process for lactate influx into muscle tissue are difficult to evaluate. As an approximation, Watt et al. (85) assessed the effects of perfusate flow on rapid tracer lactate influx into isolated, resting rat hindlimb. Rapid tracer lactate influx as measured by the paired-tracer dilution method was dependent on perfusate flow at rates less than 0.5 mL·g^{-1}·min^{-1}. However, limitations of the paired-tracer method prevent definitive conclusions.

In summary, blood flow and its optimal distribution are theoretically of great importance in net lactate exchange. In the case of net lactate uptake, if all other factors remain constant, an increased blood flow should increase lactate and proton delivery to the muscle, thereby maintaining more favorable extracellular to intracellular lactate and proton gradients, thus promoting net lactate uptake. Lactic acid translocation across the sarcolemma is likely to be rapid due to *trans*-stimulation or equilibrium exchange conditions between the interstitial and intramuscular spaces. However, *net* exchange will be enhanced only by maintaining a [La] *gradient* and/or a proton *gradient* (48).

BLOOD LACTATE CONCENTRATION

Radioactive tracer studies in dogs (43), rats (29), and humans (20,83) have shown that lactate uptake increases as the blood [La] increases. Pagliassotti and Donovan (67) obtained similar results in perfused muscles of the rabbit. Their results, with a special emphasis on fiber type, are discussed in more detail in another paper in this symposium by Donovan (24).

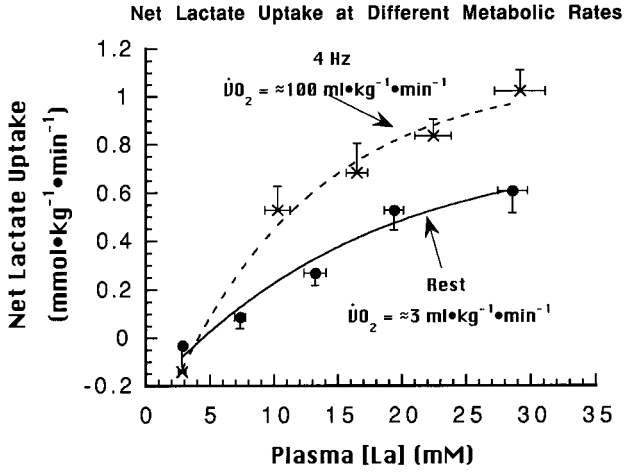

Figure 2—Net lactate uptake by canine gastrocnemius *in situ* at rest and during contractions (twitches at 4 Hz) at a high metabolic rate with increasing plasma [La]. [Redrawn with permission from Gladden, L. B., R. E. Crawford, and M. J. Webster. Effect of lactate concentration and metabolic rate on net lactate uptake by canine skeletal muscle. *Am. J. Physiol.* 266: R1095-R1101, 1994 (35).]

In addition, Gladden et al. (32,34,35,37) have shown that net lactate uptake by canine gastrocnemius muscle *in situ* increases in proportion to arterial plasma [La]. Figure 2 (35) illustrates that progressively increasing plasma [La] elevated net lactate uptake, with a tendency for net lactate uptake to approach a plateau at the higher plasma lactate concentrations (≈20–30 mM). The highest asymptote for net lactate uptake was calculated for twitch contractions at a frequency of 4 Hz. This contraction frequency produces $\dot{V}O_{2peak}$ for twitches in this muscle preparation (13). Interestingly, the asymptote for peak net lactate uptake (1.1 mmol·kg^{-1}·min^{-1}) in these twitch contractions is only half the peak net lactate output (2.2 mmol·kg^{-1}·min^{-1}) measured during contractions that elicit tetanic $\dot{V}O_{2peak}$ (13,51). There are several possible reasons for this large difference. First, it is likely that net lactate uptake during the twitches was limited by lactate metabolism within the muscle. There would be no analogous limitation for net lactate output. Also, a more favorable duty cycle for blood flow (12,13,23,51) could have promoted lactate output in the tetanic contractions in comparison to the net lactate uptake during the twitch contractions. Perhaps net lactate uptake during the twitches was limited by membrane transport of lactate. If so, there may have been a greater transmembrane [La] gradient in the experiments with net lactate output during tetanic contractions. There may also have been a greater [H^+] gradient in the direction of lactate translocation during the tetanic contractions. It is unlikely that asymmetry of the lactate transport processes causes a faster efflux in comparison to influx (33,46–48). All of these possible differences between tetanic lactate output and twitch lactate uptake point to a need for experiments in which net lactate uptake is assessed with elevated blood [La] during steady state tetanic contractions.

Considering the effect of [La] on membrane transport, it has been well established that transmembrane lactate flux is dependent on the transmembrane [La] gradient. This is apparent as a linear, diffusive component in addition to a saturable component which is the result of monocarboxylate transport protein (MCT) activity (46,48,74,77,78,86). Sarcolemmal lactate transport is described in detail by Bonen (7) in a separate paper of this symposium.

HYDROGEN ION CONCENTRATION

Possible effects of [H^+] on lactate utilization are most likely related to intramuscular (intracellular) [H^+]. It is a reasonable assumption that *if* increased intracellular [H^+] inhibits lactate production in the presence of an adequate exogenous [La], then lactate utilization will be enhanced. In support of this notion, Graham et al. (39) reported that acidosis, induced by hypercapnia, resulted in net lactate uptake by dog gastrocnemii *in situ* after 20 min of contractions at 3 Hz. Under normal acid-base conditions, the gastrocnemii were still releasing lactate after 20 min of contraction at 3 Hz. Bonen et al. (11) have also reported that glycogen synthesis from lactate in mouse fast-twitch (EDL) and slow-twitch (soleus) muscles *in vitro* was stimulated by decreases in external pH over the physiological range. Whether this enhancement of glyconeogenesis was due to a reduced intracellular pH that inhibited PFK activity thus promoting reversal of glycolysis or was due to a greater transmembrane [H^+] gradient that increased membrane transport of lactate is unclear. Further study of the interaction between intracellular [H^+] and lactate utilization is needed.

Roth and Brooks (79) have shown that the absolute [H^+] is of little consequence to sarcolemmal lactate transport. However, increases in the [H^+] gradient across the sarcolemma stimulate flux in the direction of high [H^+] to low [H^+] although the reported magnitude of the effect has varied (9,46,48,50,61,62,79,86). If the direction of the [H^+] gradient is counter to the [La] gradient, lactate flux is markedly inhibited (79). Two mechanisms explain the stimulatory lactate transport effect in the direction of a proton gradient. First, diffusion of lactate occurs primarily in the form of undissociated lactic acid (HLa) and is therefore mainly dependent on the concentration of HLa (46,50,79). By the law of mass action, HLa concentration ([HLa]) on the side of higher [H^+] will be increased in comparison with [HLa] on the side of lower [H^+].

Second, a proton gradient probably also stimulates lactate transport via its effect on the monocarboxylate carrier. As Figure 3 illustrates, H^+ probably binds to the carrier first and then the lactate anion follows (8,48). Unloading occurs in the reverse order. In this scheme, high protons on one side of the membrane would speed H^+ binding to the carrier and therefore speed lactate binding. On the low [H^+] side, H^+ unloading after lactate unloading would be enhanced. The effect of proton gradients most likely depends on the combination of the proton gradient and the [La] gradient and therefore the relative contributions of diffusion versus carrier to lactate flux.

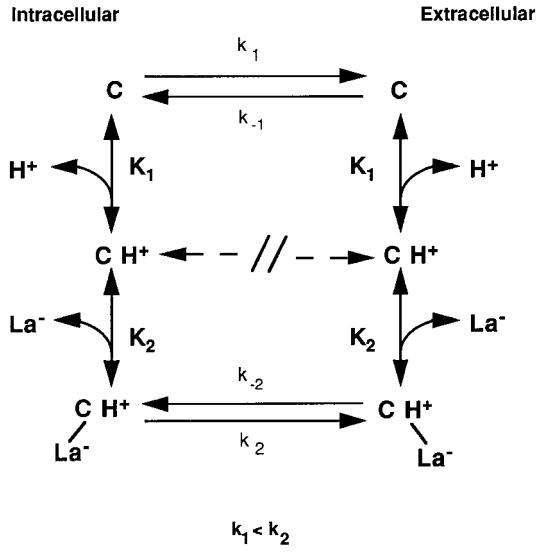

Figure 3—Diagram of proposed model for the monocarboxylate carrier of lactate transport in red blood cells (74). Lactate transport in sarcolemmal vesicles has been proposed to be qualitatively similar (46,74). The different K's represent binding rates, whereas the k's represent translocation rates. Apparently the carrier binds H^+ first and then lactate. The carrier with only H^+ bound is believed to be either immobile or else translocates only very slowly. [Redrawn with permission from Poole, R. C., and A. P. Halestrap. Transport of lactate and other monocarboxylates across mammalian plasma membranes. *Am. J. Physiol.* 264: C761-C782, 1993 (74).]

MUSCLE FIBER TYPE

Net lactate uptake and disposal. Donovan (24) addresses the role of muscle fiber type in the net fate of lactate taken up by muscles in another paper in this symposium. Therefore, only a brief summary will be provided here. Oxidative muscle fibers begin to take up lactate at a lower perfusate or blood [La] and take up lactate at faster maximal rates in comparison to glycolytic muscle fibers (33,66,67). Oxidative muscle fibers predominantly oxidize lactate whereas glycolytic fibers primarily convert lactate to glycogen (2,11,33,63,66–68,80). Lactate oxidation is highly correlated with the total LDH H-isozyme activity (2). Both the rate of muscle lactate uptake and the route of disposal for lactate clearly depend on the fiber type composition of the muscle (33).

Lactate transport. Only a few studies (9,49,72) have investigated lactate transport in different muscle fiber types, but the findings are consistent. Lactate transport is significantly faster (≈37–109%) in oxidative muscle fibers than in glycolytic fibers. Bonen (7) will provide details on the lactate transport protein in another paper in this symposium. However, it should be noted here that Bonen's group (58) has shown that muscle content of the Type I monocarboxylate transporter (MCT1) is highly correlated with the percentage of oxidative fibers in the muscle.

At first glance, the finding that lactate transport is faster in oxidative muscle fibers than in glycolytic fibers contradicts the notion that glycolytic muscle fibers are prone to high lactate production rates during contractions/exercise and that they should be equipped for rapid transport of lactate out to the extracellular environment. However, oxidative fibers do produce lactate and they are usually active for longer periods of time than are glycolytic fibers. A greater ability to transport lactate (and H^+ ions at the same time) out of oxidative fibers might partially explain the greater resistance to fatigue in oxidative fibers (49). Further, peak lactate production by oxidative muscle fibers may be greater than is usually appreciated. For example, peak lactate output by contracting, oxidative canine gastrocnemius muscle *in situ* is similar to peak lactate output by contracting, glycolytic feline gastrocnemius muscle *in situ* (82). Juel (48) notes that if the metabolic ability of muscle fibers to produce lactate is based only on muscle lactate concentration without considering release, differences in maximal lactate production between glycolytic and oxidative muscle fibers may be overestimated. Finally, the faster lactate transport rates in oxidative fibers may reflect the role of lactate as an energy substrate for those fibers, whereas the slower lactate transport rates in glycolytic fibers may contribute to greater retention of lactate during recovery from intense exercise. The retained lactate in glycolytic fibers postexercise is then more likely to be resynthesized into glycogen (67–69).

EXERCISE TRAINING

Lactate metabolism. Endurance training appears to cause an increase in lactate utilization by muscles. Several studies in rats (25–27) as well as humans (55,70) have reported that metabolic clearance rate of lactate is significantly increased after endurance training. Presumably, most of this clearance enhancement is due to adaptations in skeletal muscle. As an example, Donovan and Pagliassotti (27) infused lactate into resting rats at different rates. With increasing rates of lactate infusion, blood [La] rose in a curvilinear fashion, reaching >11 mM in sedentary rats as compared with ≈5.5 mM in endurance trained rats. As shown in Figure 4, this training response was due to a more rapid rise in net lactate removal with increases in blood [La]. The apparent Km for net lactate removal was dramatically lowered after training to a value that was one-third that found in the sedentary animals (4 vs 12 mM).

The mechanisms underlying improved lactate removal by muscle after endurance training are not well-defined. Training-induced metabolic adaptations in skeletal muscle that might be expected to speed lactate utilization include: 1) increased oxidative capacity due to a greater mitochondrial content causing increased oxidative enzyme concentrations, 2) increased pyruvate dehydrogenase activity that could improve pyruvate usage after its production from lactate, 3) increased malate-aspartate shuttle activity that might facilitate oxidation of NADH resulting from lactate to pyruvate conversion, and 4) a shift in the lactate dehydrogenase isozyme pattern from the muscle isoform toward the heart isoform (26,27).

Lactate transport. There is almost unanimous agreement that muscle activity pattern (i.e., muscle unweighting, denervation vs chronic stimulation, exercise training) influences lactate transport across the sarcolemma, sometimes

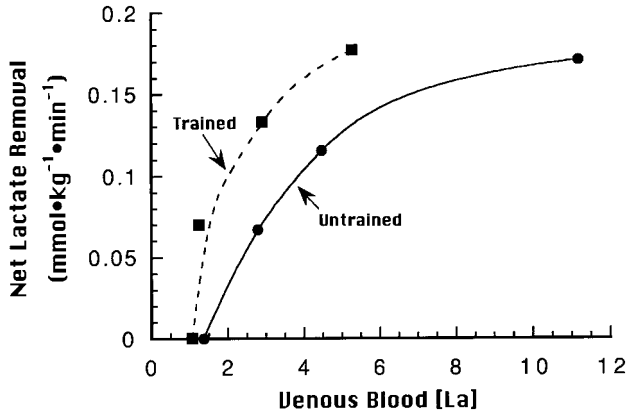

Figure 4—Net lactate removal at different steady state venous blood lactate concentrations in anesthetized rats that were either untrained (control) or endurance trained. [Redrawn with permission from Donovan, C. M, and M. J. Pagliassotti. Enhanced efficiency of lactate removal after endurance training. *J. Appl. Physiol.* 68:1053–1058, 1990 (27).]

quite dramatically (1,28,56,57,59,60,71,73). The largest changes in lactate transport (2–2.8× increase) have been observed after 7 d of chronic electrical stimulation of tibialis anterior muscles of the rat (57,59). However, the *pattern* of reported effects is not consistent. Among those studies that have made estimates of the kinetics of lactate transport, exercise training has been postulated to lower the Km and increase the V_{max} (73), or to reduce the Km with no effect on the V_{max} (60). Most of these kinetics values represent crude estimates based on only a few [La] gradients and sometimes on data patterns that do not appear to follow Michaelis-Menten kinetics. Some of the apparent discrepancies may arise from differences in experimental procedures, such as the gender of animals studied, training programs, and methods of lactate transport measurement.

There has been only one study of the effect of training on sarcolemmal lactate transport in humans. Mean lactate efflux rate was significantly higher from the sarcolemmal giant vesicles of athletes as compared with vesicles from untrained and trained control groups. However, no subject with $\dot{V}O_{2max}$ less than 68 $mL \cdot kg^{-1} \cdot min^{-1}$ had a greater than average lactate transport capacity. Specific comparisons among the athletes revealed that both a high volume (frequency and duration) and regular high intensity of training were required to improve lactate transport capability. The highest lactate efflux rates were found in two 4-km bicyclists, one of whom was a bronze medalist at the 1992 Olympic Games.

The reported improvements in lactate transport ability due to increased muscle activity could result from an increase in the percentage of slow twitch, oxidative muscle fibers (48,71,73). However, it seems more likely that increased substrate affinity of the carrier ($\downarrow$ Km), increased intrinsic activity of the carrier ($\uparrow V_{max}$), increased density of carriers in the sarcolemma ($\uparrow V_{max}$), or changes in the isoform distribution of the carrier ($\downarrow$ Km and/or $\uparrow V_{max}$) could account for the changes (48,57,59,60,73).

The underlying stimulus for the transport alterations is clearly related to the repeated contractions. However, it is unlikely that the stimulus is increased glycolytic activity and concomitant changes in tissue [La] (48,57). Regardless of causation, improved membrane transport of lactate could promote lactate efflux from muscles that are producing lactate, and aid influx into less active muscles for oxidation and/or glyconeogenesis (33,48,60).

SUMMARY

In summary, the evidence suggests that net consumption of lactate by skeletal muscle is likely to be enhanced by:

1) A high steady-state metabolic rate that does not engender an elevated endogenous lactate production that interferes with exogenous lactate utilization. Effects of increased metabolic rate on sarcolemmal lactate transport appear to be minimal.

2) Blood flow that is adequate to maintain optimal outside to inside [La] and [H^+] gradients. The blood flow should ideally be matched to the rate of net lactate uptake; that is, the L/Q ratio should be optimized. Whether or not higher than normal spontaneous blood flow will facilitate lactate exchange is not clear.

3) An elevated [La] gradient at least to the point of saturation of either the metabolic pathways for lactate utilization or the sarcolemmal monocarboxylate transport system. Whether metabolism or transport is the key limiting factor is not known.

4) An increased intracellular [H^+] to the extent that it inhibits endogenous lactate production without inhibiting muscle function or limiting inward sarcolemmal lactate transport. Probably more importantly, a significant outside to inside [H^+] gradient will stimulate sarcolemmal lactate influx.

5) A predominance of oxidative muscle fibers. Oxidative muscle fibers are metabolically tuned for lactate oxidation and have a greater capacity for sarcolemmal lactate transport than do glycolytic muscle fibers.

6) Endurance training. Metabolically, endurance training improves muscle capacity for lactate utilization. In terms of membrane transport, increased muscle activity has a positive impact but whether or not this impact is realized in humans except under conditions of both high volume and high-intensity training is not clear.

THE NEXT CHALLENGE

Presently, we know a great deal about the processes involved in lactate exchange, including the various pathways of metabolism and the sarcolemmal transport process. However, we do not know exactly how lactate exchange is regulated under various conditions. Specifically, what role if any does the MCT family play in the regulation or limitation of net lactate exchange?

Typically, if a [La] gradient across a membrane is observed, it is inferred that there is a transport limitation. Although this may be the case, it is not necessarily true that unidirectional lactate flux is limiting just because a [La] gradient exists. For example, it has been proposed that

lactate is distributed as an inverse function of the transmembrane [H^+] ratio (76). If true, this could be due to the fact that transport via diffusion depends on the concentration of the undissociated lactic acid ([HLa]), which increases as the [H^+] increases and/or the fact that MCT transport of lactate is enhanced in the direction of the [H^+] gradient due to a faster binding of H^+ to MCT (see section on Hydrogen Ion Concentration above). At least one implication of this hypothesis is that even in a steady state in which the net lactate flux is zero and transmembrane lactate translocation is not limiting, the intracellular and extracellular concentrations of lactate are unlikely to be equal. Is it possible that cellular pH regulation drives steady state transmembrane lactate distribution? However, Juel (48) presents strong arguments (which will not be repeated here) in favor of the notion that transmembrane lactate distribution is a function not only of the [H^+] gradient but also of blood flow and the balance between lactate transport and metabolism (see Juel's review, ref. 48, pp. 333–339 and associated citations).

Based on the evidence to date, it seems most likely that lactate transport is limiting during and after high-intensity exercise. Under such conditions, the rate of lactate production apparently outstrips maximal net efflux of lactate (48). Whether or not membrane transport of lactate limits net lactate uptake is less certain. It is a universal finding that intramuscular [La] is lower than external [La] during periods of elevated perfusate or blood [La] (3,21,32,37,52,63,76). The ratio between intracellular [La] and extracellular [La] covers a broad interval with several reported values in the range of 0.4–0.6 (3,32,37,48,37). Does this mean that lactate transport is limiting? Again, at least a portion of this [La] gradient may be attributable to the prevailing [H^+] gradient (31,76) or alternatively to the balance between net lactate influx and intramuscular lactate removal due to metabolism (48). For working hearts using lactate as a major energy source, Halestrap et al. (40) have estimated that lactate influx may exceed the maximal capacity of MCT. However, if diffusive flux is included, transport may not be limiting. Recent reports from Bonen's laboratory (1,7,8,10,59) relative to the effects of chronic muscle stimulation and exercise training on muscle MCT1 content lend credence to the notion of a regulatory role for lactate transport *per se.*

I believe that our speculations about limiting factors for transmembrane lactate flux are being made on the basis of weak or nonexistent data. I am unaware of any studies that have validly evaluated intracellular, interstitial, and plasma lactate concentrations under a variety of physiological conditions. A careful determination of intracellular to extracellular [La] ratios requires as a minimum accurate measurements of total muscle water, interstitial water, and plasma water along with rapid separation of plasma from red blood cells. This would allow correction of measured muscle [La] for interstitial lactate *assuming that interstitial [La] is equal to plasma [La]*. However, a) interstitial [La] may not always be equilibrated with plasma [La] (48,54), and b) interstitial [H^+] may also be different from plasma [H^+] (31,84).

How can we assess the possible role of lactate transport as a limiter of lactate exchange and metabolism? Sarcolemmal vesicles offer many advantages: a) they allow studies of sarcolemmal transfer alone, b) they eliminate confounding problems of metabolism, capillary diffusional resistance and flow, interstitial concentration variabilities, and uncontrolled intracellular solute compositions, and c) they have provided the material for isolation, purification, and sequencing of the lactate transporter protein (33,48,77,78). However, sarcolemmal membrane preparations represent only a small sample of the total membrane surface. Also, they separate the lactate transport processes from the metabolic processes that they serve. This removes regulatory interaction between transport and metabolism (33,62). Some questions regarding lactate transport require models other than sarcolemmal vesicles. For example, there is presently no way to estimate the physiological lactate transport capacity from vesicle studies. Furthermore, experiments with sarcolemmal vesicles do not provide any method for direct evaluation of the possible effects of physiological factors such as blood flow, muscle contractions, and changes in hormonal concentrations on the lactate transport process.

Promising possibilities are offered by multiple tracer methods and models such as those developed by Bassingthwaighte's group (4,5,53). These techniques employ realistic and necessarily complex models of capillary-tissue exchange. One such model is the MMID4 model (6); that is, *M*ultiple path, *M*ultiple tracer, *I*ndicator *D*ilution, *4* region model (see Bassingthwaighte et al. (6) for illustration and details). Data collection is similar to that of the less precise paired tracer technique (36,42,87) except that an intravascular tracer is used as well. Ideally, comprehensive data collection (including microsphere measurement of blood/perfusate flow heterogeneity) will allow quantitative, accurate estimation of capillary permeability, sarcolemmal permeability, and rapid metabolism of lactate. Typical data are

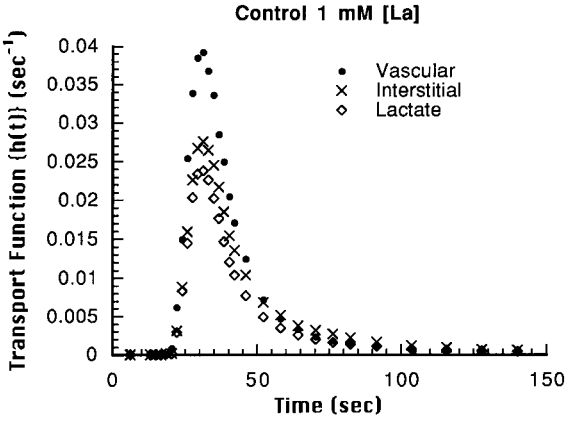

Figure 5—Venous outflow dilution curves for radioactive albumin ([^{125}I]albumin = Vascular marker), L-glucose (L-[^{3}H]glucose = Interstitial space marker), and lactate (L-[^{14}C]lactate = permeant tracer of interest) from surgically isolated canine gastrocnemius *in situ*. The transport function (h(t)) is the fraction of the total radioactive dose injected into the arterial inflow that is appearing in the venous outflow per second: $h(t) = {}_1F_BC(t)/q_o$ where F_B is the perfusate flow through the muscle (mL·s^{-1}), q_o is the quantity of tracer injected (μCi), and C(t) is outflow concentration of the tracer in venous outflow at time t (μCi·mL^{-1}). Unpublished data of Gladden et al.

presented in Figure 5. Although modeling and parameter estimation have not yet been done, there does appear to be measurable lactate influx that is inhibited by the lactate transport blocker PCMBS. Preliminary results suggest that metabolism of lactate to CO_2 and H_2O accounts for less than 5% of the counts throughout the lactate curve. It also appears that only a small amount of the counts are attributable to pyruvate (<5%). Perhaps this model as well as other experimental approaches will provide information on the possible regulatory role of lactate transport in the near future.

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Address for correspondence: L. Bruce Gladden, Department of Health & Human Performance, 2050 Memorial Coliseum, Auburn University, Auburn, AL 36849-5323; E-mail: gladdlb@auburn.edu.

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