The Lactate Paradox in Human High-Altitude Physiological Performance

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For many years, physiologists have puzzled over the observation that, during maximum aerobic exercise, high-altitude natives generate lower-than-expected amounts of lactate; the higher the altitude, the lower the postexercise blood lactate peak. This paradoxical situation may be caused mainly by upregulated metabolic control contributions from cell ATP demand and ATP supply pathways.

Anyone who has journeyed into mountains that are ≳2,000 m high will have a sense of how debilitating hypobaric hypoxia can actually be; and, of course, the higher we go, the more severe the hypoxia, and the more debilitating the effects on our physiology and performance. Many of us also know that, after some period of time at altitude, these effects are to some degree alleviated. Even more disturbing on such excursions into high altitudes are our observations of the performance of native highlanders, who seem to be far less debilitated than we might expect based on our own feelings of malaise. This is common if anecdotal knowledge for most of us, and it represents surprisingly accurately the field of play for the disciplines of high-altitude biology, physiology, and medicine. Many of the human hypoxia defense responses that help to explain the above anecdotal insights are now well known and appear to be regulated by control systems initiated by at least several oxygen-sensing and signal transduction systems (9, 20). These hypoxia response systems, which in sum may be thought of as a high-altitude physiological phenotype (9), are well known and are not controversial. In contrast, one aspect of lactate metabolism, frequently termed the lactate paradox, has remained quite controversial.

Defining the lactate paradox

The whole field of lactate metabolism in high-altitude conditions has been perplexing to physiologists for two reasons. First, it was often noted in high-altitude natives that the higher the altitude (i.e., the greater the degree of hypoxia being experienced), the lower the peak, postexercise blood lactate concentrations ([lactate]) during a given exercise protocol. This observation on high-altitude natives, first noted over a half century ago, has been perplexing to physiologists: because less lactate is found under more and more O2-limiting conditions, the phenomenon became known as the lactate paradox (7, 8, 19).

The mechanisms underlying this phenomenon remain unclear. To physiologists, there was a second reason for being perplexed, namely the observation, frequently reported, of attenuation of lactate accumulation during hypoxia acclimation despite maintained hypoxia. The origin of the hypoxia-acclimation-induced lowering of peak blood [lactate] relative to levels in acute hypoxia is, so far, poorly understood. A key point is that the acclimation response is included in the definition of the so-called lactate paradox. Thus, to avoid confusion, it is important to emphasize the two aspects to the definition of the lactate paradox: 1) the lower-than-expected accumulation of blood lactate in VO2 max tests in native highlanders compared with lowlanders and 2) the lower-than-expected accumulation of blood lactate in VO2 max tests in hypoxia-acclimated lowlanders compared with patterns found in unacclimated or acute hypoxia responses. These patterns are summarized by West (19) and Hochachka (7, 8).

The lactate paradox is a graded, not an all-or-nothing phenomenon

It is important to note that, as in many physiological characters, the above exercise-lactate patterns actually represent graded, rather than all-or-none, responses. A recent study of native Tibetans compared with lowland Han, for example, indicates that on average at altitude the Tibetans display the lactate paradox, but there is a great deal of overlap in peak [lactate] in the two groups (6). Recently, Saltin and his coworkers (14) studied a group of Europeans that were acclimated to ~5,000 m altitude in the Bolivian Andes. They found that the high blood [lactate] accumulated at in situ hypoxic conditions was essentially the same as postexercise peak lactate values found during acutely imposed breathing of air enriched with oxygen. These protocols (transitions from hypoxia to hyperoxia) were the “mirror” image of most experiments designed to expose the acclimation aspect of the lactate paradox (transitions from normoxia to hypoxia) but were nevertheless interpreted to indicate that the lactate paradox could be contravened. At the March 1999 International Hypoxia Symposium in Canada, these kinds of data provoked so much controversy that “metabolism” researchers were challenged to “find the answer to the paradox.” For this reason, the main focus of the current paper is to review the nature of this problem, trying to develop a broader understanding and a theoretical framework that might be able to accommodate both the original and these
Peak [lactate] could be influenced by production/release into plasma or by uptake from plasma

In considering mechanisms underlying the lactate paradox, the first thing to emphasize is that peak [lactate] following exercise could be influenced either by changes in production (mainly by working muscles), then release, into the plasma; by changes in lactate uptake (and subsequent metabolism) by various tissues; or by both processes occurring at once. The balance between production and uptake has been carefully analyzed (4); although both processes were involved, at submaximal exercise the effect of lactate uptake rates on plasma [lactate] tended to dominate the picture. Under VO$_2$ max protocols, however, as muscles may be making more and more lactate, lactate release (rather than uptake) may well dominate peak lactate profiles. High lactate production may be due to (5–10%) contributions of anaerobic glycolysis and glucose metabolism (18) or due to aerobic overproduction of pyruvate and subsequent conversion to lactate (5). Studies of dog leg muscle preparations (see Ref. 8 and references therein) have shown that, even when oxygen is nonlimiting, the higher the work rate the higher the rate of muscle production and release of lactate. High rates of lactate production under otherwise aerobic high work rate conditions and accounting for up to 20% of total ATP turnover have subsequently been confirmed for several human and animal muscles by using noninvasive magnetic resonance spectroscopy (MRS) techniques (5). For these reasons, and because lactate, fuel selection, and exercise have been reviewed (3), in this analysis we will focus mainly on regulation of lactate production and its influence on the so-called lactate paradox.

Metabolic controls on lactate production and accumulation during exercise

For many years, metabolic biochemists have appreciated that lactate can be generated under both aerobic and anaerobic conditions (4, 5, 7, 10). Our problem is to decipher the mechanisms that nature uses to control these kinds of metabolic processes; how, in other words, the many biochemical and physiological steps are linked together to form coordinated metabolic and physiological function regulated in vivo. Although the concept of a single rate-limiting process (acting like a valve) remains widely accepted in biology, by the mid-1960s metabolic researchers had abandoned this concept in favor of multiple contributors or of multiple sites sharing in control of the overall process (10, 13, 16). To evaluate the varied contributions to overall control of flux (J$_{\text{max}}$), say of carbon substrates in metabolic pathways, experimenters examine the fractional change in J$_{\text{max}}$/fractional change in flux capacity through any given step or process in the metabolic pathway under consideration. Such fractions for different steps in the overall pathway are termed control coefficients (13). Researchers examining the sharing of control at physiological levels frequently refer to “conductance of” or “resistance to,” for example, O$_2$ flux at different steps (lungs, circulation, etc.) in the path for O$_2$ from air to mitochondria [see Jones (12) and references therein]. Quantitative control analyses of metabolic pathways (13, 16) and of in vivo physiological systems (12) are discussed elsewhere. Suffice it here to emphasize that the principle of shared control is common to both metabolic pathway and in vivo physiological models (5, 10) and that directions of change in control contributions in different physiological states can be evaluated qualitatively. For example, if the O$_2$ diffusion capacity of the lung is increased by 50% but only a 25% change in overall net O$_2$ flux is observed, the control coefficient for the lung is 0.5, equal to the fractional change in J$_{\text{max}}$/fractional change in lung O$_2$ diffusion capacity. Similar considerations apply to all other steps in integrated pathways, and all of the control coefficients in the pathways by definition add up to 1. In a system with a classic single rate-limiting step, say O$_2$ delivery, the control coefficient for that step would be essentially 1; i.e., all control vested in this process (10, 12, 13, 16).

For elite mammalian and human athletes under normoxic conditions, significant contributions to control of ATP turnover at VO$_2$ max have been estimated for O$_2$ delivery steps (alveolar ventilation, pulmonary diffusion, heart and circulation), for aerobic cytosolic/mitochondrial metabolism, for anaerobic glycogenolysis, and for actomyosin and Ca$^{2+}$-ATPases (10, 12). How similar or different might the control features of exercise energy turnover be in native highlanders? If we use normoxic lowlanders as the reference against which to compare highlanders, we can easily identify the direction in which the control contribution of each step in energy turnover has been adjusted. Thus, in terms of such relative capacity for function, in high-altitude Quechus alveolar ventilation, pulmonary diffusion capacities, and circulatory O$_2$ delivery capacities are distinctly upregulated. However, VO$_2$ max in these subjects is notably downregulated (9, 20). Thus we can by definition conclude that the control coefficients of all of the above O$_2$ delivery steps will be depressed in high-altitude natives relative to normoxic lowlanders. On the other hand, mitochondrial ATP synthase capacities (mitochondrial volume densities), anaerobic glycolytic enzyme potentials, and muscle mass (hence total muscle actomyosin and Ca$^{2+}$-ATPase capacities) are distinctly downregulated in high-altitude natives (8, 9, 20), generally in step with the decline in VO$_2$ max and in glycolytic function (lactate production). Thus, in contrast to the lung, heart, and circulation, the control coefficients of cell ATP synthesis and ATP demand pathways are relatively higher than in normoxic lowlanders. Compared with muscle work in lowlanders, in exercising high-altitude natives muscle ATP demand and supply pathways were earlier described as being more tightly coupled (7, 15). Most telling is the insight (8, 10, 16) that improved ATPase-linked ADP control may underlie improved homeosta-

"...how...the many biochemical and physiological steps are linked together to form coordinated metabolic and physiological function...."
sis of metabolite intermediates, as observed (7, 9, 15) for phosphocreatine (PCr), inorganic phosphate (Pi), adenylates, and lactate, in endurance athletes and in high-altitude natives during muscle exercise.

We can deduce similar trends in hypoxia acclimation, even if not enough data are available for quantitative metabolic control analysis as can be used in simpler systems (13, 16). Again using lowlanders as a reference point, in humans acclimated to hypobaric hypoxia, the control coefficients for the above O2 delivery pathways are expected to decrease. This is because ventilation and circulatory O2 delivery capacities are upregulated while $\dot{V}_{\text{O2 max}}$ indexed by VO2 max is downregulated (8–10); hence fractional change in $\dot{V}_{\text{O2 max}}$/fractional changes in flux capacities of each of the above processes must decrease. Simultaneously, the control coefficients for muscle ATP synthesis pathways and for ATP demand pathways are expected to rise (10), since these processes are modestly downregulated during hypoxia acclimation (recall that the sum of these control coefficients always is 1). Recent metabolic control studies (5, 7–10, 16) in fact indicate that, when coupled to ATP hydrolysis, both the fermentation of glycogen (glucose) to lactate and the oxidation of these carbon sources are stimulated by ADP and Ca2+ (linked to actomyosin ATPase and Ca2+-ATPase functions, respectively). For activation of aerobic or anaerobic glycolysis, ADP concentration ([ADP]) must rise into the 100- to 300-M range, whereas for activation of mitochondrial metabolic pathways [ADP] in the 30-M range will do (5, 7, 8, 10, 15). When comparing acclimated to nonacclimated individuals at VO2 max, like in the above evaluation of control in Andean natives, these moderate adjustments in energy supply-energy demand pathways should also allow for improved metabolite homeostasis during exercise metabolism.

With respect to lactate, the key insight arising is that glycolytic and oxidative pathways are in part controlled by the action of ATPases. The better this control, the lower the perturbation during exercise of adenylates and of other intermediates in the above metabolic pathways (15, 16), the lower the signal explaining why in several biological situations an inverse relationship occurs between change in [PCr] and change in [lactate] or [H+]. A particularly striking example is the fast-twitch epaxial muscles of tuna during recovery (Fig. 1), where these relationships are maintained over a concentration range of nearly 120 mM lactate (2). From these data, it is easy to conclude that the same set of causal relationships may underlie peak lactate patterns in exercising humans under differing conditions and, though overlooked by earlier workers, may indeed underlie the so-called lactate paradox.

One such overlooked example comes from our own earlier studies of Sherpas (1), considered by many physiologists as the most exquisitely high-altitude-adapted of all humans so far studied. In these 31P MRS studies, PCr and H+ were monitored simultaneously and, though overlooked by earlier workers, may indeed underlie the so-called lactate paradox.

The evidence for this interpretation arises from 31P MRS studies of working calf muscles indicating that ATP demand and ATP supply pathways are better coupled in high-altitude natives and in endurance-trained athletes (15) than in sedentary lowlanders or power-trained lowlanders. Although unclear to us earlier on, we now believe that the data are robust enough to essentially prove that the above model is basically correct. This is because layered on the above metabolic pathways is a biochemical indicator of the very processes that are regulating lactate production. The indicator is creatine phosphokinase (CPK), a so-called near-equilibrium enzyme, which, because of its high turnover number per catalytic site and high concentration, is able to hold the CPK reactants at close to equilibrium concentrations at all times (1, 5, 8, 10). Furthermore, the hydrolysis of CPK is coupled to glycolysis through ADP and ATP as well as through $H^+$ (formed during in vivo glycolysis) according to the equation $H^+ + PCr + ADP \leftrightarrow ATP + creatine$. If our hypothesis of the lactate paradox mechanism is correct, the CPK “window on metabolism” would predict a direct relationship between [lactate] and [ADP] and an inverse relationship with PCr concentration ([PCr]). Since [ADP] can be buffered by other reactions and cannot be interrogated non-invasively, our test of the model depends on an inverse relationship with PCr concentration ([PCr]) and [lactate] or [PCr] and $H^+$ concentration ([H+]). Although $H^+$ and lactate are produced in a 1:1 stoichiometric relationship, 31P MRS assays only the former; because $H^+$ is buffered, quantification of lactate by measuring $H^+$ involves some uncertainty (5). Still, for comparative purposes, especially on a constant buffer background, the direction of change can be unequivocally determined. In fact, we have argued elsewhere (2, 8, 10) that the above relationships explain why in several biological situations an inverse relationship occurs between change in [PCr] and change in [lactate] or [H+]. A particularly striking example is the fast-twitch epaxial muscles of tuna during recovery (Fig. 1), where these relationships are maintained over a concentration range of nearly 120 mM lactate (2). From these data, it is easy to conclude that the same set of causal relationships may underlie peak lactate patterns in exercising humans under differing conditions and, though overlooked by earlier workers, may indeed underlie the so-called lactate paradox.

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**FIGURE 1.** Simultaneous measurements of muscle phosphocreatine (PCr) and lactate concentrations during recovery from fatigue in tuna. Unlike most teleosts, which require 8 h or more to clear maximum lactate loads after vigorous swimming, this species is able to return to preexercise conditions in ~90 min. By standards of the vertebrate world, tuna are outstanding in being able to accumulate muscle lactate to >100-mM concentrations. Over this entire range, there is an inverse relationship between lactate and PCr concentrations. See Ref. 2 for experimental details.
are expressed as percentage of total areas under the PCr, Pi, and ATP peaks; [H+] was estimated from chemical shift differences between mono- and diprotonated inorganic phosphate (Pi). During the first work bout (20% of maximum), there is no relationship between [PCr] and [H+]; presumably, at this time the known ATP demand-supply imbalances and increases in [ADP] shifted the CPK equilibrium and so caused an observed decrease in [PCr]. At the next two workloads (at 30 and 40% of maximum), there was a clear-cut inverse relationship between decreasing [PCr] and increasing [H+], just as would be predicted by the above theory.

In such MRS studies, the relationship between PCr and lactate is sometimes easier to display in recovery from exercise than during exercise per se (in part because the signal/noise ratio is often better because the interrogated muscle is not moving). For example, Matheson et al. (15) compared the recovery patterns of PCr and H+ in gastrocnemius of four subject groups: Andean highland Quechusas, sedentary (European origin) lowlanders, power-trained individuals, and endurance-trained subjects. In addition to a reduced perturbation of the adenylates and [PCr] at VO2 max, they found that the fastest recovery patterns for both PCr and H+ occurred in the endurance-trained and in Andean groups, followed by power-trained individuals and finally by sedentary subjects.

To emphasize functional significance, the time required for PCr resynthesis to reach an arbitrary value (0.7 fraction of the total phosphate pool (PCr + Pi + ATP)) is plotted against the intracellular pH in the muscle at the same time point (Fig. 3). As can be seen, the two parameters are very closely related. Since H+ is used here and elsewhere (1, 5, 11, 15) as a surrogate measure of lactate, we tentatively conclude that fast PCr recovery correlates with low peak lactate observed in these Quechusas and vice versa for slower recovery. As above, it is clear that this is a graded, not an all-or-nothing, phenomenon, which is why we propose that the lactate paradox itself is a graded phenomenon. That this is not unique to this data set is indicated by the following study on muscles of lowland individuals (European origins).

In this study, each subject worked to volitional fatigue using a calf muscle ergometer fitted to a wide-bore 3-T magnet; localized 31P MRS was utilized to follow [PCr] down to ~5% of resting values. Following a 5.5-min period of imposed ischemic fatigue, the muscle was allowed to recover. Although these experiments were designed with different goals in mind (10, 17), they nevertheless showed that subjects with highest VO2 max showed the most rapid PCr recovery, and we consider it fairly safe to assume that the fast PCr recovery correlates with lower peak [lactate], as above.

Model to explain varying peak lactate patterns in VO2 max tests

If the above analysis is correct, it suggests that there is a (probably state-specific) relationship between muscle ADP and...
glycolytic flux, which is reflected in the inverse [PCr] vs. [lactate] or [PCr] vs. [H+] in these various metabolic states. Under conditions such as VO2max testing, when peak plasma [lactate] are probably largely dominated by muscle production (5, 7, 18), we in fact predict the fundamental PCr-lactate and PCr-H+ relationship that is observed. When different kinds of subjects are compared in this kind of plot (low- vs. high-altitude natives, before vs. after high-altitude acclimation, before vs. after endurance or power training), their differing biochemistry and physiology should move peak lactate values up or down along the general relationship shown in Fig. 4 (the exact slope would almost certainly be species and state specific, depending on intracellular buffering and intracellular phosphagen concentrations). If correct, this summary model goes a long way toward explaining the current, seemingly discordant data in the literature. Most instructive, it supplies a unified explanation for a wide variety of patterns that have been previously reported but that to this point have remained largely unexplained.

Summary

The main functional advantages of the lactate paradox (maintained metabolite homeostasis at fatigue, quicker recovery, and avoidance of overactivation of energetically inefficient anaerobic metabolism in hypobaric hypoxia) have long been recognized (10, 11, 20), but underlying mechanisms have remained obscure. From these kinds of studies, it appears that the mechanistic basis for lower muscle lactate production in high-altitude natives at their maximum aerobic work rate is caused mainly by upregulated control contributions from cellular ATP demand and ATP supply pathways (with downregulated control coefficients for all of the major steps in O2 delivery). This allows for improved coupling between ATP demand and supply pathways, for improved metabolite homeostasis (including adenylates and lactate), and for lower concentrations of glycolytic activators such as ADP under VO2max conditions. The key insight, that lactate production is a function of how metabolic and physiological control contributions are organized in the complex pathways of ATP supply and demand, should be generally applicable to muscle during exercise in many differing physiological states. For native highlanders showing lowlander control features, the peak lactate patterns would be like those of lowlanders, and vice versa. The same would be true when comparing hypoxia-acclimated vs. nonacclimated subjects or subjects in varying, or different kinds of, training states. In other words, the lactate paradox is a graded, not an all-or-nothing, phenomenon. Once understood, it is a paradox only in name.

Finally, we should emphasize that the hypoxia acclimation responses of native highlanders are not as robust as those of lowlanders. Indeed, in at least some Andean natives, the lactate paradox does not change even after 6 wk of acclimation to changed altitude conditions (11), suggesting that in some metabolic characteristics “once a highlander, always a highlander.” In general, it is known that allelic differences account for ~30–70% of the variance in physiological traits, so genetic contributions to these phenotypes are pretty well assured (9). Using modern molecular tools, a search has been made for genotypes (or for genotype markers) underlying these metabolic phenotypes, but thus far with no major success. In fact, what these studies mostly show is that the gene markers examined are remarkably conserved in highlanders and lowlanders (9, 10).

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References


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