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INVITED REVIEW

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Lactate during exercise at high altitude

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Abstract In acclimatized humans at high altitude the reduction, compared to acute hypoxia, of the blood lactate concentration (la) at any absolute oxygen uptake ($\dot{V}O_2$), as well as the reduction of maximum la (la_{max}) after exhaustive exercise, compared to both acute hypoxia or normoxia, have been considered paradoxical, and these phenomena have therefore become known as the "lactate paradox". Since, at any given power output and $\dot{V}O_2$, mass oxygen transport to the contracting locomotor muscles is not altered by the process of acclimatization to high altitude, the gradual reduction in $[la^-]_{max}$ in lowlanders exposed to chronic hypoxia seems not to be due to changes in oxygen availability at the tissue level. At present, it appears that the acclimatization-induced changes in $[la^-]$ during exercise are the result of at least two mechanisms: (1) a decrease in maximum substrate flux through aerobic glycolysis due to the reduced $\dot{V}O_{2max}$ in hypoxia; and (2) alterations in the metabolic control of glycogenolysis and glycolysis at the cellular level, largely because of the changes in adrenergic drive of glycogenolysis that ensue during acclimatization, although effects of changes in peripheral oxygen transfer and the cellular redox state cannot be ruled out. With regard to the differences in lactate accumulation during exercise that have been reported to occur between lowlanders and highlanders, both groups either being acclimatized or not, these do not seem to be based upon fundamentally different metabolic features. Instead, they seem merely to reflect points along the same continuum of phenotypic adaptation of which the location depends on the time spent at high altitude.

Key words Exercise · Glycolysis · Catecholamines · Muscle · Fatigue · Human · Native

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Introduction

During graded exercise (e.g. running or cycling), the blood lactate concentration ($[la^-]$) attained at the steady-state of each power output ($\dot{W}$) increases with the exercise intensity. This is due to a change in the equilibrium between lactate appearance (production and washout) and lactate removal (uptake and utilization). In fact, lactate production during the transient phase at the onset of exercise increases with exercise intensity (Cerretelli et al. 1979), to be later compensated for by a corresponding increase in lactate removal, so that at steady-state exercise higher stable $[la^-]$ values are observed (Brooks 1986). This equilibrium is lost during high-intensity exercise when lactate production exceeds lactate removal and $[la^-]$ keeps increasing with time. The increased lactate removal from the blood results from uptake and increased oxidation of lactate, which takes place either in organs such as the liver, or in the muscles themselves ("lactate shuttle", see, e.g. Brooks 1986). Under certain circumstances, contracting muscles may even take up lactate produced elsewhere (Brooks et al. 1991a).

The relationship between $[la^-]$ and $\dot{W}$ is curved, with an increasing slope for an increasing $\dot{W}$. This particular shape, with an inflection point ("lactate threshold"), has been attributed to various mechanisms: a reflection of the onset of a lack of oxygen in the contracting muscle; an increase in the recruitment of fast-twitch fibres at high $\dot{W}$; an increased reliance on carbohydrates; the energy state of the cell; and increasing levels of circulating hormones like adrenaline. The premise that an increase in $[la^-]$ during exercise of increasing intensity reflects tissue hypoxia is no longer widely accepted (Brooks et al. 1991b; Connet et al. 1990; Gollnick and Hermansen 1973). Even though it is beyond doubt that severe tissue hypoxia and/or ischaemia do lead to increased lactate production, the literature shows that lactate production occurs continuously under aerobic conditions. In any case, the modulation of lactate pro-

duction and utilization is complex and depends on many regulatory mechanisms. During exercise one important modulation is through adrenaline that, via β-receptors in muscle, can initiate a cascade of events stimulating the degradation of glycogen, leading to a higher glycolytic flux (Chasiotis 1985). For a given rate of pyruvate removal into the Krebs cycle, this leads to a higher pyruvate-to-lactate flux through the mass effect.

In acute hypoxia, the relationship between [la^-] and $\dot{W}$ is shifted upwards and to the left, implying higher lactate levels at any given $\dot{W}$, whereas the maximum [la^-] ([la^-]$_{max}$) is similar compared to that measured in normoxia (Cerretelli et al. 1982; Edwards 1936) (see also Fig. 1). By contrast, in chronic hypoxia, the relationship between [la^-] and $\dot{W}$ is intermediate between that measured in acute hypoxia and in normoxia. But since maximum oxygen consumption ($\dot{V}O_{2max}$) and maximum power output are decreased, [la^-]$_{max}$ is also lower (Bender et al. 1989, Cerretelli et al. 1982; Edwards 1936; Grassi et al. 1995; Grassi et al. 1996; Kayser et al. 1993b; West 1986). In high altitude-acclimatized subjects, this reduction of [la^-]$_{max}$ after exhaustive exercise, compared to that measured during acute hypoxia or normoxia, and the reduction, compared to that in acute hypoxia, of [la^-] at the same absolute $\dot{V}O_2$, even in the presence of an unchanged oxygen delivery to the exercising muscles, have been considered "paradoxical" (Hochachka 1989; Reeves et al. 1992; West 1986). The aim of this article is to briefly review this phenomenon, now also known as the "*lactate paradox*".

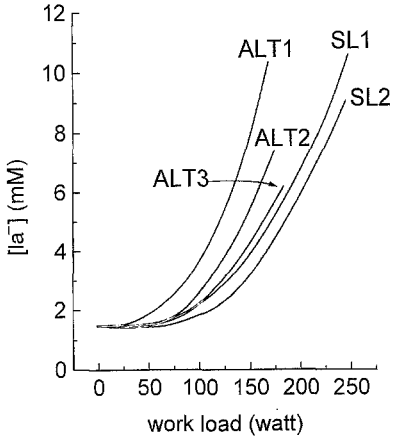

Fig. 1 Blood lactate [*la*$^-$] versus work load during symptom-limited incremental cycle exercise in lowlanders at sea level (*SL1*), at 5050 m upon arrival (*ALT1*), and after 3 weeks (*ALT2*) and 5 weeks (*ALT3*), then 1 week after return to sea level (*SL2*). Notice that at *ALT1* the maximum [la^-] ([la^-]$_{max}$) is similar to that at sea level (*SL1*) but attained at a lower work load. With acclimatization, the curves (*ALT2* and *ALT3*) tend towards *SL1*, and [la^-]$_{max}$ is progressively decreased and attained at slightly higher work loads. On return from high altitude the curve (*SL2*) is initially to the right of that prior to exposure (*SL1*) and only returns to *SL2* over a 6-week deacclimaization period. (Redrawn using data from Grassi et al. 1996)

Lactate at high altitude: the early observations

The first observations of blood [la^-] during exercise at high altitude were made by Dill et al. (1931). At high altitude, at a given sub-maximum mechanical power output, [la^-] initially rose higher than at sea level but, after acclimatization, reached sea-level values again. Edwards (1936) reported higher [la^-] levels at sub-maximum power outputs in subjects acutely exposed to high altitude as well, but he also found that [la^-]$_{max}$ was similar compared to that measured at sea level. After acclimatization, [la^-] levels at sub-maximum power outputs had returned close to sea-level values, whereas [la^-]$_{max}$ had decreased. Edwards thought that the decrease in [la^-]$_{max}$ during acclimatization to high altitude might be explained by the reduced alkali reserve, by an altered enzyme activity, or by early exhaustion from diaphragmatic fatigue (Edwards 1936). Cerretelli (1967) showed that the decreased alkali reserve at high altitude, from the hyperventilatory metabolic-compensated respiratory alkalosis, indeed shifts the slope of the line relating the exercise-induced increase of [H^+] to that of [la^-] in blood and he argued that a lower intracellular pH for a given [la^-] could possibly impair the activity of glycolytic enzymes like phosphofructokinase (PFK), at an earlier stage than at sea level, a hypothesis taken up again by West in 1986.

A paradox?

Since its introduction in 1989, considerable confusion has arisen as to exactly what is understood by the term "lactate paradox". Historically, the word paradox in connection with lactate at high altitude was introduced by West in 1986. He measured a partial pressure of carbon dioxide in arterial blood (P_aCO_2) on Mt. Everest of 100 Pa (7.5 Torr) and calculated a resting P_aO_2 of 3.73 kPa (28 Torr), implying an even lower value during exercise. Despite this extreme hypoxaemia, no lactate accumulation would take place when extrapolating West's graph (adapted from Cerretelli 1980) (Fig. 2): "If this extrapolation held good, a well-acclimatized climber who reached the summit of Mount Everest without supplementary oxygen would have no blood lactate. This is a paradox indeed, because such a climber is apparently more hypoxic during maximal exercise than in any other known situation" (West 1986). In contrast with this prediction, during Operation Everest II (OE-II, a simulated climb of Mt. Everest), it was observed that exhausting exercise at a pressure equivalent to that at the summit of Mt. Everest resulted in a small, but significant, increase in blood [la^-] over resting values (Sutton et al. 1988; Young et al. 1992).

The term "lactate paradox" was introduced by Hochachka (1989). He defined it as: "during incremental aerobic exercise tests to fatigue under hypoxic conditions they (the Quechuas, South-Americans native to

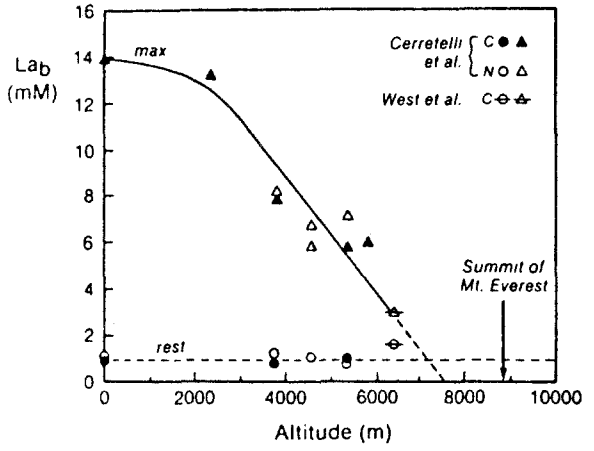

Fig. 2 The original figure from West (1986). Maximal blood lactate (La_b) as a function of altitude. Most of the data are redrawn from Cerretelli et al. (1982). The *filled circles* and *triangles* show data for acclimatized Caucasians (*C*); the *open circle* and *triangles* are for those natives to regions of high altitude (*N*). The data for 6300 m are from acclimatized lowlanders (reproduced with permission)

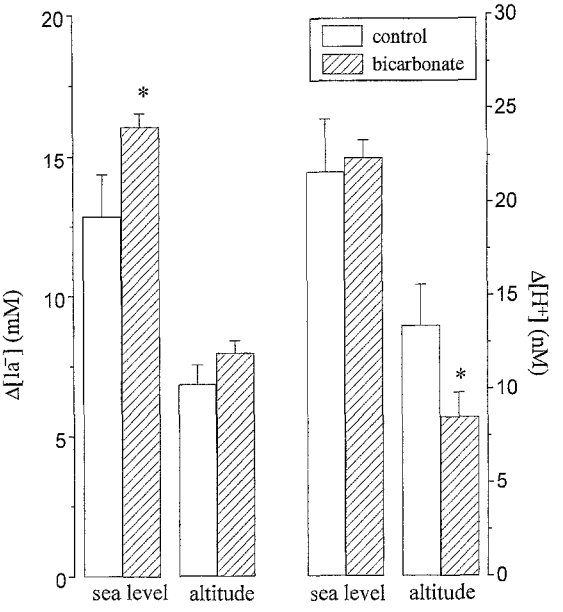

Fig. 3 The average net increase in maximal lactate concentration ($\Delta[la^-]_{max}$), and net increase in proton concentration ($\Delta[H^+]$), measured at the end of exhausting maximal exercise at sea level and after 4 weeks at high altitude (5050 m). Values are means (SD), with and without prior bicarbonate ingestion (3 g/kg body mass). At sea level an increased buffer capacity allowed an increase in time to exhaustion, and an increase in $\Delta[la^-]$, whereas at high altitude, despite a normalized buffer capacity, time to exhaustion did not change, $\Delta[la^-]$ remained below sea level values, and $\Delta[H]^+$ decreased. Decreased buffer capacity thus does not seem to be limiting $[la^-]_{max}$ at high altitude.* $P<0.05$. (Redrawn from Kayser et al. 1993)

the high altitudes of the Andes) form less lactate and accumulate it to lower levels than normoxic lowlanders" (Hochachka 1989). After 6 weeks of deacclimatization at sea level, these subjects were still unable to accumulate as much lactate as lowlanders during exhausting cycling exercise and he concluded (Hochachka 1989) that it was therefore the expression of a fixed metabolic feature ("the perpetual lactate paradox"). Perhaps the more appropriate definition was that recently proposed by Reeves et al. (1992), in a review of data obtained from lowlanders during OE-II and during work carried out on Pike's Peak, Colo., USA. They defined the lactate paradox as the situation: "in which blood lactate accumulation during exercise is increased on arrival at high altitude but falls with acclimatization", the paradox being that this occurs without a concomitant change in muscle oxygen delivery since the increase in haemoglobin concentration, and therefore oxygen concentration of arterial blood, is offset by a reduction in muscle blood flow.

Recent observations

Buffer capacity

The buffer capacity hypothesis (Cerretelli 1967; Edwards 1936; West 1986), based on the altitude-induced loss of carbon dioxide and bicarbonate stores of the body, was tested at 5050 m during exhausting exercise at $\dot{V}O_2max$, with and without prior oral sodium bicarbonate ingestion (Kayser et al. 1993b). Despite normalized buffer stores after bicarbonate ingestion (3 g/kg body mass) at altitude, $[la^-]_{max}$ levels did not increase and, at exhaustion, exercise was interrupted with both muscle and blood pH still higher than at sea level (see Fig. 3). This hypothesis was therefore rejected.

Substrate availability

With regard to substrate availability, the muscle resting glycogen level seems barely affected by chronic hypoxia (Green et al. 1989; Young et al. 1982). Upon arrival at high altitude, a standardized exercise causes a glycogen depletion somewhat greater than at sea level, but after acclimatization the depletion is the same again as at sea level (Green et al. 1992). This muscle-glycogen-sparing effect upon acclimatization was attributed to a lesser β-adrenergic-mediated stimulation of glycogenolysis (Brooks et al. 1991c, see also below) and to a lesser dependence on intramuscular glycogen sources (Brooks et al. 1992; Green et al. 1992), compared to that during acute hypoxia. In any case, a lack of muscle glycogen stores does not seem to be the basis of the changes in lactate which occur during exercise at high altitude.

Enzyme activity

The activity of several glycolytic enzymes in the vastus lateralis muscle of climbers after a 6 to 8-week exposure to altitude at 5000–8600 m was essentially unchanged compared to pre-exposure (Howald et al. 1990), which confirmed earlier results, including data

relating to total glycogen phosphorylase (Green et al. 1989; Young et al. 1984). A slight decrease in PFK activity at 4300 m was found, but that was explained as a consequence of a changed control of glycolysis rather than a cause (Green et al. 1992). By and large, it seems that the main regulatory enzymes of the glycolytic pathway are not affected by chronic hypoxia. But since enzyme activity is measured using homogenized muscle tissue in vitro, it can only partially describe regulatory metabolic mechanisms in vivo and the hypothesis that a modulation of enzymatic metabolic control of glycogenolysis or glycolysis may be the basis of the changes in lactate appearance during exercise at high altitude cannot be ruled out. Indeed, even if total muscle glycogen phosphorylase is not altered at altitude (Green et al. 1992; Young et al. 1984) it remains possible that an increased activation of phosphorylase *b* to its active form phophorylase *a*, for example during the initial phase at high altitude when adrenaline levels are high, may lead to increased glycogenolysis.

β-Adrenergic drive

After 18 days of acclimatization at 4300 m, a decrease in the net lactate release from exercising legs was observed compared to that at the beginning of the sojourn at high altitude (Bender et al. 1989). However, the design of that study did not allow a distinction to be made between a reduced production or an increased removal of lactate. Recently the net rates of appearance and disappearance of lactate and glucose at rest and during standard sub-maximal exercise at sea level and at 4300 m were determined (Brooks et al. 1991b, c, 1992; Green et al. 1992; Mazzeo et al. 1994). By infusing isotope-labelled lactate and glucose, and sampling arterial as well as effluent blood from the limbs, these authors were able to measure the net release and uptake of lactate and glucose by the limbs. Acute exposure to high altitude increased the rate of lactate appearance, whereas acclimatization decreased it again. The authors proposed that this may have been related to the circulating adrenaline levels in the different experimental conditions. At the same absolute $\dot{V}O_2$, and hence the same substrate flux through oxidative phosphorylation as compared to that at sea level, acute exposure to hypoxia increases adrenaline release, which would stimulate glycogenolysis and glycolysis, leading to increased lactate release (Brooks et al. 1992). With acclimatization, adrenergic drive would subside and the stimulation of glycolysis would decrease. This train of thought is based on the fact that the sympathetic system is known to modulate glycogenolysis and thus the influx of glucosyl monomers into glycolysis. Adrenaline binds to β-receptors in the muscle, thereby, through a second messenger system [adenosine 3,5,-cyclic monophosphate (cAMP)], activating a kinase (Chasiotis 1985). The latter subsequently transforms phosphorylase *b* into its active form, phosphorylase *a*, which is the enzyme controlling the rate of glycogen splitting to glucosyl monomers. At sea level, infusion of adrenaline at rest indeed increases the activated fraction of phosphorylase from 28% to 88% (Ren and Hultman 1990). Since acute hypoxia, per se, increases arterial catecholamine levels during exercise (Mazzeo et al. 1991), it thus seems likely that glycolysis would be stimulated. During sustained sub-maximal bicycle exercise, both at sea level and high altitude, the rate of lactate appearance in the blood as well as arterial [la^-], are closely related to the level of adrenaline in the blood, indeed suggesting a causal relationship between adrenergic drive and [la^-] (Brooks et al. 1992; Mazzeo et al. 1991; Reeves et al. 1992). Interestingly, the changes in the levels of circulating catecholamines at high altitude follow different patterns (Mazzeo et al. 1991). Noradrenaline levels were similar at sea level and upon acute exposure to 4300 m, but were increased after 21 days of chronic exposure. By contrast, resting arterial adrenaline values during acute and chronic exposure both exceeded those at sea level. Values during exercise upon arrival were greater than those at sea level but fell after 21 days. The level of noradrenaline during exercise was related to systemic vascular resistance, whereas the level of adrenaline was related to the concentration of circulating lactate. It was concluded that during exercise at high altitude there is a dissociation between noradraline, an indicator of sympathetic neural activity, and adrenaline, an indicator of the adrenal medullary response. It was hypothesized that these actions may account for different metabolic and physiological responses to acute versus chronic exposure to high altitude. In another study, unacclimatized subjects, who were receiving the β-blocker propanolol, had low blood [la^-] levels upon arrival at 4300 m, similar to those of acclimatized subjects (Young et al. 1991). In that study it was concluded that the higher [la^-] values observed during exercise at sub-maximal work loads during the initial phase at high altitude result, at least in part, from increased β-adrenergic stimulation. Unfortunately, in the latter study, the subjects worked at the same relative power output (80% of $\dot{V}O_2max$) and effects dependent on the absolute level of $\dot{W}$ could not be excluded. In a recent study, the power output was standardized ($\approx$50% of sea level $\dot{V}O_2max$) and a close relationship was again found between the concentration of adrenaline and [la^-] (Brooks et al. 1992; Mazzeo et al. 1994). In that experimental set-up, β-blockade did indeed attenuate the amplitude of the effect of acute exposure to high altitude on glycolysis, and blood [la^-] was lower than in the control condition, although still higher than at sea level. β-Blockade, however, did not fully prevent the progressive decrease in blood [la^-] during exercise that accompanies acclimatization to high altitude, although the amplitude of the decrease was considerably less (Mazzeo et al. 1994). Thus, even though in acute hypoxia an adrenaline-mediated increase of glycolysis appears to take place, since β-blockade could not completely abolish the progressive

reduction in [la^-] at a given power output that occurs with acclimatization, it was concluded that the acclimatization-induced changes in lactate during exercise cannot be fully explained by an alteration of adrenergic control of glycolysis alone (Mazzeo et al. 1994). This is not so surprising since it is an oversimplification to attribute to β-receptor binding by adrenaline and subsequent activation of phosphorylase *all* modulation of glycogenolysis. Although glycogenolysis is indeed controlled by phosphorylase *a*, activation of phosphorylase *alone* is not sufficient to increase the glycogenolytic rate. Even in the presence of fully activated phosphorylase, only when the muscle contracts does glycogenolysis substantially increase (Ren and Hultman 1990). Increased concentrations of Ca^{2+} ([Ca^{2+}]), inorganic phosphate ([P_i]) and adenosine monophosphate ([AMP]) probably all play a role. It seems that the rate of glycogenolysis during muscular contraction is determined by the turnover rate of adenosine triphosphate (ATP) rather than [P_i]. Small increases in [AMP] may occur in contracting muscle, which could be of importance in regulating phosphorylase activity and consequently controlling the rate of glycogenolysis (Ren and Hultman 1990).

Mass oxygen transport

Classically the accumulation of lactate during exercise at sea level as well as at high altitude was interpreted as being the consequence of insufficient availability of oxygen at the tissues. This concept has been severely challenged in favour of a significant lactate production also occurring in aerobic conditions (Brooks 1991a; Connet et al. 1990; Gollnick and Hermansen 1973). In acclimatizing subjects at 4300 m, during sub-maximal exercise, blood flow to the exercising legs appears to be regulated to maintain oxygen transport constant, thereby matching oxygen supply to demand (Wolfel et al. 1993). The increase in arterial oxygen concentration from the acclimatization was off-set by a drop in muscle blood flow. Mass oxygen transport to, and oxygen consumption by, the limb were thus the same in acute and chronic hypoxia and, in addition, muscle stores of ATP and phosphocreatine (PCr) were well maintained. Muscle oxygen insufficiency therefore seemed to be neither the cause of the increased arterial [la^-] in acute hypoxia, nor that of the subsequent decrease observed upon acclimatization (Wolfel et al. 1993). On the whole, at high altitude the changes in lactate metabolism during exercise that ensue from acclimatization appear to be unrelated to changes in oxygen availability at the tissues (Reeves et al. 1992). However, it cannot be excluded that, even in the presence of an unchanged oxygen delivery, an improved oxygen conductance from the blood to the mitochondria may play a role (Grassi et al. 1996). Increases in capillarization, myocyte myoglobin concentration and blood haemoglobin content would, in fact, all favour oxygen transfer.

Central drive and peripheral fatigue

During OE-II, at low barometric pressures, bicycle exercise induced exhaustion with fewer biochemical signs of muscle fatigue than at sea level (Green et al. 1989). In the same study, electrical stimulation of the tibialis anterior muscle showed that the muscle compound waves (M-waves) were preserved, evidencing normal neuromuscular transmission (Garner et al. 1991). This was subsequently confirmed in a study of the monosynaptic H-reflex and the M-wave of the electrically stimulated human soleus muscle in acclimatized subjects at 5050 m (Kayser et al. 1993). The recruitment curves of both responses were obtained by stimulating the posterior tibial nerve at different intensities while recording the electromyogram of the soleus muscle at its surface. From the electromyogram, the net alpha-motoneuron excitability (ratio of maximal H-reflex to M-response, H_{max}:M_{max} ratio), the threshold and gain for both responses, as well as the latency times were determined. Since the latency times of both reflexes were unaltered at high altitude compared to at sea level, the signal conduction velocities through the different parts of both pathways were unaltered and, therefore, nerve conduction velocity as well as synapse and muscle end-plate transmission appeared not to be changed by prolonged exposure to high altitude. Those results indicated that the intrinsic properties of the different components of the two pathways were preserved. The gain of the H-response was slightly higher at high altitude when compared to that at sea level, indicating that the recruitment of the H-reflex was slightly facilitated after acclimatization to high altitude. This suggested an increased excitability of the alpha-motoneurons through either post-synaptic facilitatory changes in the soma or a different descending drive. The unchanged H_{max}:M_{max} ratio indicated no change in the net excitatory and inhibitory influences on the alpha-motoneuron pool. Using a different protocol, muscle force, relaxation rate and fatigue properties were studied during voluntary and electrically evoked isometric contractions of both the adductor pollicis and quadriceps femoris muscles (Kayser et al. 1993c). Supramaximal percutaneous electrical stimulation was used to investigate the frequency/force (f/F) relationship and maximum relaxation rate. The f/F relationships and maximum relaxation rate were essentially unchanged during the 4-week sojourn at 5050 m. No changes occurred in the maximum voluntary contraction force (MVC) or in the tetanic force at 100 Hz (F_{100Hz}), suggesting a maintained ability for full activation of motor units. During OE-II, several subjects showed signs of reduced motor drive while doing MVCs at extreme simulated altitude However this could be overcome by volition upon strong verbal encouragement (Garner et al. 1991). Taken together, it would thus appear that the function of the neuromuscular system does not seem to be affected (Garner et al. 1991; Kayser et al. 1993a, c). In principle, the muscle should thus be able to perform normally. However,

whereas, during a 1-month sojourn at 5050 m, all-out vertical jumps on a force platform showed no changes in maximal explosive power output (which indicates integrity of the neuromuscular apparatus, a maximum central motor drive and maximum rates of ATP and PCr splitting) the longer duration power output of big muscle groups was reduced significantly (Kayser et al. 1994).

At sea level heavy exercise to exhaustion is limited to a large extent by the development of peripheral metabolic fatigue. Bigland-Ritchie and Vollestad (1988) hypothesized that at high altitude a decreased central drive limits dynamic exhaustive exercise with large locomotor muscle groups before peripheral metabolic fatigue can develop. Those authors hypothesized that a maximally stressed respiratory system could, via the central nervous system, limit the central drive to large muscle groups before their full potential is reached. Some evidence for this hypothesis was provided by an experiment in which acclimatized subjects at 5050 m could sustain maximum aerobic exercise with a small muscle group (forearm flexors) at the same absolute load, for the same time and with similar signs of peripheral fatigue as at sea level, whereas exhaustion of maximum cycling exercise, although performed at a lower absolute, but the same relative, load compared to sea level, was reached after a similar time, but with no signs of peripheral fatigue in the legs (Kayser et al. 1994, see Fig. 4).

In a study of subjects who were acclimatized to 5050 m, and, exercising at the same relative load as at a sea level, i.e. 75% of $\dot{V}O_{2max}$, the ventilatory system indeed appeared to be pushed to its limits, due to an extremely high ventilatory demand (Cibella et al. 1992; Kayser et al. 1993b). Despite a 23% lower absolute workload at high altitude, the time of endurance was reduced significantly (by 55%). Ventilation increased much more at high altitude than at sea level (+72%) and the respiratory rate showed a similar increase (+41%). At high altitude there was a more significant drop in diaphragmatic electromyographic centroid frequency, and inspiratory gastric pressure swings became negative shortly before exhaustion. Since both findings are suggestive of diaphragm fatigue, the latter could thus potentially provide an input to the central nervous system, leading to a decrease in central drive to the active locomotor muscles before they can develop peripheral metabolic fatigue, as suggested by Edwards in as early as 1936. However, another recent experiment performed at 5200m does not seem to support this hypothesis. Acclimatized subjects performed repeated maximal isometric voluntary contractions with the forearm flexors, before and during exhausting bicycle exercise with and without 4% inspiratory carbon dioxide. With added carbon dioxide ventilation was higher, whereas the MVC force at exhaustion was unchanged. The investigators concluded that no decrease in central drive to the respiratory muscles or locomotor muscles had occurred (Savard et al. 1996). Based on observations of

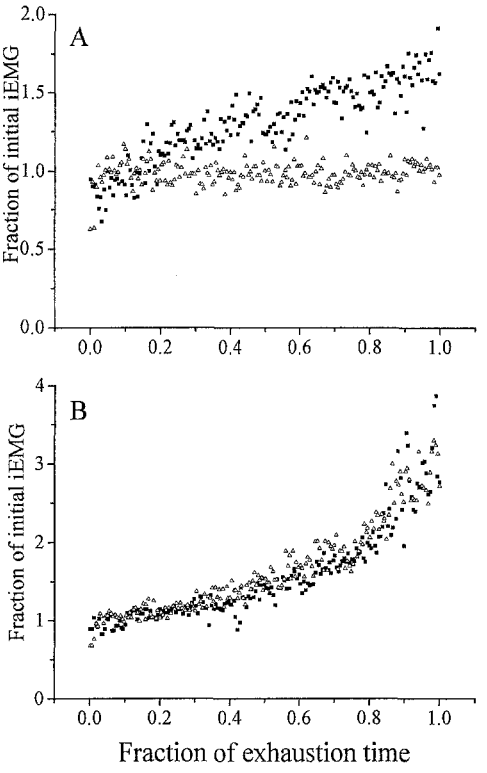

Fig. 4A,B Integrated electromyogram (iEMG) of the vastus lateralis muscle during cycling at maximum oxygen consumption ($\dot{V}O_{2max}$) (**A**) and of the arm flexor muscles during maximum dynamic forearm exercise (**B**). (*Filled squares* Sea level before departure, *open triangles* after 1 month at 5050 m). Data are from 6 subjects, but for clarity only every 10th point is shown. The increases in iEMG were accompanied by significant decreases in centroid and mean power frequencies of the EMG power spectrum, indicating the development of peripheral fatigue. Contrary to the arm flexor and vastus lateralis muscles at sea level, at high altitude the vastus lateralis muscle did not fatigue, yet exercise had to be stopped because of exhaustion, suggesting that the full potential of the locomotor muscles could not be used because of a reduced central drive. (redrawn from Kayser et al. 1994)

Indian soldiers suffering from pulmonary oedema evoked by high altitude, an interesting hypothesis was recently proposed by Paintal (1995). He argues that the hypoxic pulmonary arterial constriction at high altitude, combined with an exercise-induced additional rise in pulmonary arterial pressure and flow, may lead to sub-clinical interstitial oedema and therefore activation of the pulmonary J-receptors. These juxta-capillary receptors, sensitive to pressure as well as to interstitial oedema, would give rise to dyspnoea, via the vagus, and could, via a reflex, limit central motor drive. To date, however, there are no hard data to support this contention. Thus, the origin of the signals leading to the cessation of the central drive at exhaustion from heavy leg exercise at high altitude remains unclear. The respiratory and/or other higher nervous centres, with or without the contribution of fatigued respiratory muscles, pulmonary receptors, and/or of decreased arterial oxygen saturation, are all possible candidates. In any case, the proposed mechanism of early central limita-

tion is compatible with the absence of signs of peripheral fatigue at the end of exhausting maximum exercise with large muscle groups at high altitude and also with the lower levels of $[la^-]_{max}$ reached.

Using a short-burst-type supramaximal cycle exercise protocol of varying duration, Grassi et al. (1995) recently measured the maximum rate of lactate accumulation in arterialized blood. They found a significant reduction at high altitude and argued that this may indicate an "upstream" inhibition of glycolysis; upstream, because it would be changes in the substrate flux upstream from pyruvate that determine the changes in pyruvate-to-lactate flux at high altitude. Both the reduction in adrenergic stimulation of glycogenolysis and the reduction in motor output during sustained exercise with large muscle groups would be compatible with this contention. In Fig. 5 $\dot{V}O_{2max}$ and $[la^-]_{max}$ measured during OE-II (Young et al. 1992) are plotted as a function of the decreasing inspiratory PO_2 that was progressively reached during this simulated climb of Mt. Everest. From the bottom graph, where $\dot{V}O_{2max}$ and $[la^-]_{max}$ are plotted against each other, it can be seen that in these relatively well acclimatized subjects the decrease in maximum anaerobic glycolysis paralleled the decrease in maximum oxidative phosphorylation. According to the above-described hypothesis of an "upstream" inhibition of glycolysis, with increasing simulated altitude, due to a reduced motor drive, glycolysis would have been less stimulated and less substrate flux down to pyruvate would have led to less lactate being formed.

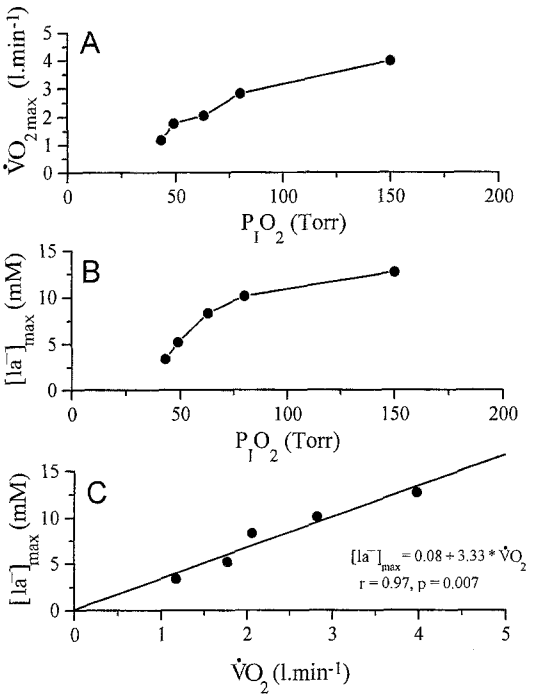

Fig. 5 Average $\dot{V}O_{2max}$ (**A**) and $[la^-]_{max}$ (**B**) versus power output at the different inspiratory oxygen pressures reached during Operation Everest II, a simulated climb of Mt. Everest. **C** $[la^-]_{max}$ and $\dot{V}O_{2max}$ are plotted against each other. The linear best fit suggests that in acclimatized subjects the reduction of $[la^-]_{max}$ is associated with the reduction in the maximum rate of oxidative phosphorylation. (Plotted using data from Sutton et al. 1988, and Young et al. 1992)

A model

Acute hypoxia

At high altitude, the power output that can be sustained for about 5 min during exercise with large muscle groups is reduced, possibly by a mechanism involving a reduction in central drive due to signals from sources other than the contracting locomotor muscles. Since the energy cost of muscular contraction per se is not altered by hypoxia, then ATP turnover, substrate flux through oxidative phosphorylation and the rate of Krebs cycling are decreased in proportion. Thus, pyruvate flux into the Krebs cycle is also decreased, simply by a mass action effect, and, if the coupling of glycolysis to oxidative phosphorylation remains constant, lactate accumulation in the blood would depend on exercise intensity and duration, and on blood lactate removal.

Lowlanders exposed to acute hypoxia react to this stressful condition with increased circulating levels of adrenaline (Mazzeo et al. 1991, 1994; Young et al. 1989, 1991). This would stimulate, through muscle β-receptors, the transformation of phosphorylase *b* to its active form, phophorylase *a*, thus, during exercise at a given load, increasing the rate of splitting of glycogen to glucosyl monomers. Since, for a given level of sub-maximal power output, ATP turnover, oxidative phosphorylation (i.e. $\dot{V}O_2$) and therefore pyruvate flux into the Krebs cycle remain constant, through a mass-action effect, disproportionately high levels of pyruvate from increased glycolysis would result in a spill-over into lactate formation, leading to higher muscle and blood $[la^-]$ levels (Brooks et al. 1991c; Green et al. 1989, 1992). During prolonged sub-maximal exercise, a new steady-state would be attained with stable, but higher, $[la^-]$ levels than in normoxia at the same $\dot{V}O_2$ (Brooks et al. 1992). For any given absolute sub-maximum power output, $[la^-]$ is thus higher than at sea level. Since at high altitude the maximum rate of oxidative phosphorylation (i.e. $\dot{V}O_{2max}$) is diminished, due to the higher glycogenolytic flux from increased adrenergic stimulation, $[la^-]_{max}$ will still reach levels similar to those observed at sea level. Even though the slope of the relationship between $\dot{V}O_2$ and power is not changed at high altitude compared to at sea level, glycolysis appears to be slightly uncoupled from oxidative phosphorylation, since for any given O_2 the $[la^-]$ levels are higher (Green et al. 1992) (also see Fig. 6). Experimental evidence for this scenario was recently presented by Hughson et al. (1995), who reported a tight relationship between catecholamines and $[la^-]$ during normoxic and acute hypoxic exercise, a relationship that was independent of the fraction of oxygen in inspired gas, F_iO_2. Interesting-

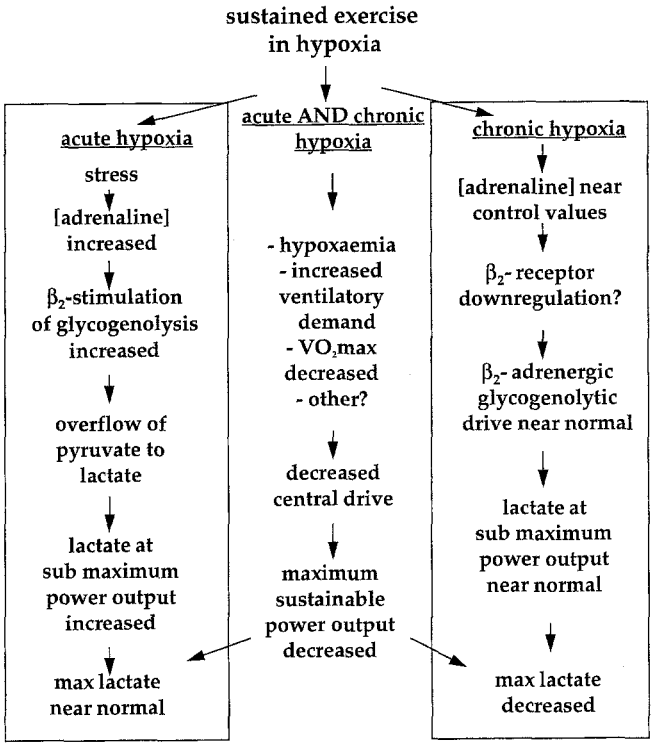

Fig. 6 A proposed model of the changes in blood lactate in lowlanders going to high altitude. The *middle panel* shows that maximum whole-body exercise capacity is decreased through a mechanism of central limitation of the sustainable maximum power output of dynamic exercise. The *left panel* explains why, through the increased adrenergic drive in acute hypoxia, increased glycolysis may still lead to high maximum lactate levels, be they at lower absolute power outputs. In the *right panel* it is shown how, in the acclimatized state, a decreased glycolytic activity in chronic hypoxia coupled to the decreased maximum power output would lead to near-normal sub-maximal, but lower maximum, blood lactate levels

ly, they also reported that at high power outputs in hypoxic conditions, $\dot{V}O_2$ was slightly lower than in normoxic conditions and that this was associated with a higher [la^-] in hypoxia than in normoxia. Those data are therefore also compatible with the dysoxia hypothesis and, apart from β-adrenergic stimulation of glycogenolysis, effects of changes in peripheral oxygen transfer and the cellular redox state may also determine the changes in [la^-] observed during exercise in acute hypoxia as opposed to normoxia.

Chronic hypoxia

After the initial increase upon acute exposure to high altitude, with acclimatization the levels of circulating adrenaline during exercise decrease again (Mazzeo et al. 1992) and β-stimulation of glycogenolysis decreases towards sea level values. In addition it is conceivable, by analogy to what happens to lymphocyte β_2–receptors and cardiac β_1–receptors (Richalet 1990), that chronic hypoxia may induce a down-regulation of β-receptors in skeletal muscle also, thereby diminishing the glycogenolytic effect of adrenaline. For a given power output and a given ATP turnover, and hence pyruvate flux into the Krebs cycle, glycogenolysis would decrease towards sea level values. This would decrease pyruvate uptake into the Krebs cycle and therefore less pyruvate would be diverted into lactate. Since $\dot{V}O_{2max}$ remains reduced compared to that at sea level, $[la^-]_{max}$ would also be reduced. Whatever the exact mechanism, in the course of acclimatization, [la^-] values attained at sub-maximal and maximal exercise intensities are lower as compared to those during acute hypoxia. As a result, glycolysis appears to be more tightly coupled to oxidative phosphorylation in chronic hypoxia than in acute hypoxia.

Since, in acclimatized subjects exercising in conditions of acute normoxia the maximum power output and $\dot{V}O_{2max}$ are increased as compared to levels measured under hypoxic conditions, one also would expect $[la^-]_{max}$ to increase. Grassi et al. (1996) recently observed that the $[la^-]_{max}$ of acclimatized lowlanders at 5050 m does not attain sea level values while the subjects were breathing an oxygen-enriched gas mixture, confirming previous observations (Cerretelli 1980; Edwards 1936). Grassi et al. (1996) also observed that $[la^-]_{max}$ only returned to pre-exposure values after 3 weeks of deacclimatization (see Fig. 7). These results suggest that, in acclimatized subjects, [la^-] is not only dependent on the rate of oxidative phosphorylation, but possibly also on other regulatory mechanisms of metabolism.

The hypotheses proposed above, which aim to account for changes in [la^-] in acute and chronic hypoxia, seem to fit the available data from the literature reasonably well. However, it should be borne in mind that the absolute [la^-] is just an epiphenomenon that results from the balance between the production of lactate in

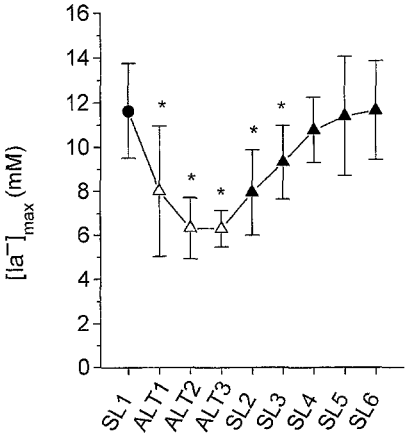

Fig. 7 Maximum blood lactate levels during incremental symptom-limited cycle exercise at sea level (*SL1*), after 1 (*ALT1*), 3 (*ALT2*) and 5 (*ALT3*) weeks at 5050 m, and after 1 (*SL2*), 2 (*SL3*), 3 (*SL4*), 4 (*SL5*) and 5 (*SL6*) weeks after return to sea level. Note the half-time of about 5 days for $[la^-]_{max}$ to attain pre-exposure levels upon return. * Different from SL1 (from Grassi et al. 1996)

blood, and its removal, both of which are controlled in many different ways. It may very well be that other mechanisms also play a role. For example, [la^-] in hypoxia is also influenced by the production and uptake of lactate in places other than the active muscles, i.e. the liver and the non-active limbs (Brooks et al. 1991b).

Lactate accumulation in populations native to regions of high altitude

Indigenous populations from mountainous areas, such as the Sherpas and Tibetans from the Himalaya or the Quechuas from the Andes, are legendary with regard to their exercise performance capacity at high altitude. Numerous studies have been done to investigate any differences between these people and acclimatized lowlanders. Since recent work on Quechuas has indicated that these people may differ from lowlanders with regard to lactate accumulation during exercise (Hochachka 1989), it seems useful to briefly review the pertinent literature. Sherpas, of Tibetan origin living in the Nepalese Himalaya, and South-American Indians are populations that are indigenous to regions of high altitude, and they are characterized by low $[la^-]_{max}$ values (about 6 mM at high altitudes of about 4000 m) (Cerretelli 1980; Cerretelli and diPrampero 1985, Cerretelli et al. 1982). Most research concerning adaptation to high altitude of populations that are native to mountainous regions has been conducted by taking scientific equipment into the field and by studying the experimental subjects in their home region. Few observations have been carried out using people brought down to sea level (Cerretelli 1980; Cerretelli and diPrampero 1985; Cerretelli et al. 1982; Hurtado 1932; Paz Zamora et al. 1982). Hochachka and colleagues changed the research strategy by taking six Quechua Indians, who were born and had lived for essentially all of their lives at high altitudes ranging from 3600 to 4500 m, to sea level (Hochachka 1989; Hochachka et al. 1991; Matheson et al. 1991). They reported that these indigenous Andean people had lower [la^-] levels in hypoxic conditions than lowlanders had in normoxic conditions. (Hochachka 1989). In lowlanders acclimatizing to high altitude, the onset of the lower $[la^-]_{max}$ has a half-time of about 5 days (Fig. 7) (Grassi et al. 1992). Upon return to sea level, normal $[la^-]_{max}$ values are attained after a few weeks, also with a half-time of ≈ 5 days (Grassi et al. 1992). Since, even after 6 weeks of deacclimatization, the Quechuas were still unable to accumulate as much lactate as lowlanders during exhausting bicycle exercise, Hochachka et al. (1991) hypothesized that the reduced [la^-] was a fixed feature of possible genetic origin.

Recent studies at high altitude, which involved endurance-trained South-American people native to regions of high altitude, showed that during exhausting cycle exercise these subjects could attain [la^-] levels around 8–10 mM, which are similar to those reported for lowlanders at sea level (Favier et al. 1995). In a corollary study these subjects did not increase the peak oxygen uptake or power output during one leg exercise only when they were acutely exposed to normoxia, presumably because they were limited by the oxidative capacity of the active locomotor muscles since mass oxygen transport was not maximal. The peak [la^-] level in blood was significantly lower in acute normoxia as opposed to chronic hypoxia, suggesting a relatively loose coupling between oxidative phosphorylation and glycolysis. The relationship between [la^-] and power output was shifted downwards in normoxia and this shift was closely correlated with changes in adrenaline concentration (Fig. 8), suggesting that the above-discussed modulation of glycogenolysis by adrenaline is also significant for those indigenous to regions of high altitude.

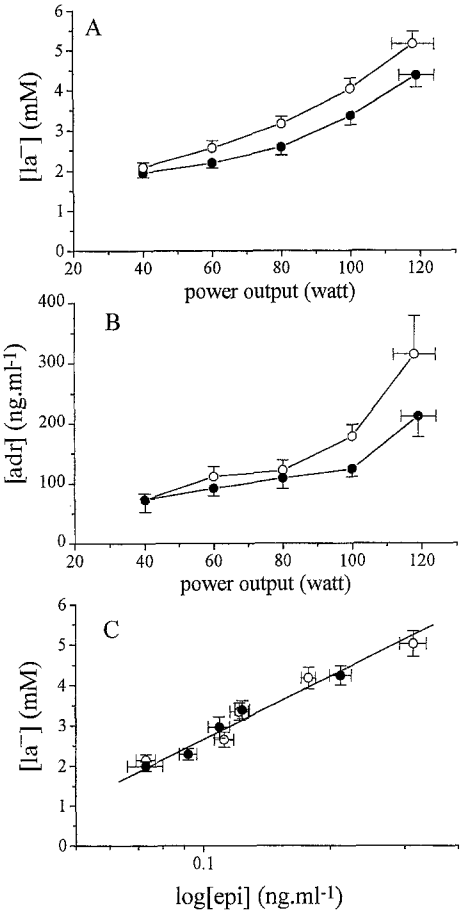

Fig. 8 Blood lactate (**A**) and adrenaline (**B**) levels versus power output in those native to regions of high altitude during one-legged exercise in chronic hypoxia (*open circles*) and acute normoxia (*closed circles*). In normoxia, lower sub-maximum and maximum lactate levels were reached at identical oxidative fluxes suggesting loose coupling of glycolysis to oxidative phosphorylation. There was no significant effect of the fractional concentration of oxygen in inspired air on the adrenaline versus lactate relationship (**C**), suggesting an adrenergic origin for the different lactate levels in the two conditions. At high concentrations there appeared to be a saturating effect of the adrenaline on [la^-], which would be in agreement with a β-receptor-mediated mechanism

At equivalent metabolic flux downstream from pyruvate (Krebs cycling), the pyruvate-to-lactate flux was not fixed, but modulated by adrenergic activity changing substrate flux upstream from pyruvate.

Tibetans, born at low altitude (1300 m, Kathmandu, Nepal) and never exposed to high altitude, but whose parents came originally from the Tibetan plateau (3500–5000 m), have the same maximum aerobic power, $[la^-]_{max}$, mechanical efficiency during cycling and the half-time of the $\dot{V}O_2$–on response at $\approx 50\%$ $\dot{V}O_{2max}$ when compared to a local lowland control group, indicating that the metabolic response to an exercise stress, in particular lactate accumulation in blood, is similar in the investigated groups (Kayser et al. 1994). Thus, the typical low $[la^-]$ levels during exercise in acclimatized subjects at high altitude are not seen in subjects who genetically are highlanders but who were born and live at low altitude. The presence of these low $[la^-]$ levels in highlanders born and living at high altitude must therefore be an acquired characteristic, as it is for acclimatized Caucasians. The fact that, for the Quechuas, it does not fully disappear within 6 weeks of the sojourn at sea level is intriguing, but this does not necessarily imply that it is a permanent feature. In lowlanders the lactate accumulation during exercise only normalizes 3 weeks after return to sea level (Grassi et al. 1992). It cannot be excluded that a deacclimatization over a longer period than 6 weeks would increase $[la^-]_{max}$ in Quechuas as well.

Conclusions

Since at high altitude and at any given whole-body exercise intensity, mass oxygen delivery to the contracting locomotor muscles is not altered by the process of acclimatization, the gradual reduction in $[la^-]_{max}$ in lowlanders exposed to chronic hypoxia seems not to be due to changes in oxygen availability in the contracting locomotor muscles, although an effect of changes in peripheral oxygen transfer and in the cellular redox state cannot be ruled out. At present it appears that the changes in the lactate accumulation pattern during exercise at high altitude are the result of at least two mechanisms: (1) a decrease in the maximum substrate flux through oxidative phosphorylation due to a reduction of $\dot{V}O_2max$ in hypoxia; and (2) alterations in the metabolic control of glycogenolysis and glycolysis at the cellular level, largely because of the changes in adrenergic drive that ensue during acclimatization. With regard to the differences in the $[la^-]$ versus power relationships and the $[la^-]_{max}$ values observed between lowlanders and highlanders, irrespective of acclimatization, these do not seem to be based on fundamentally different metabolic features. Instead, they seem merely to reflect points along the same continuum of phenotypic adaptation of which the location depends on the time spent at high altitude. In any case, the exact mechanisms defining the changes in the blood lactate level during hypoxic exercise, both in lowlanders and highlanders, are still matter for further investigation.

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