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Hormonal and metabolic adjustments during exercise in hypoxia or normoxia in highland natives

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Instituto Boliviano de Biologia de Altura, Casilla 717, La Paz, Bolivia; Unité de Recherches Associée 1341 Centre National de la Recherche Scientifique, Laboratoire de Physiologie, Université Claude Bernard, 69373 Lyon cedex 08, France; and Anatomisches Institut, Universität Bern, 3000 Bern 9, Switzerland

Favier, R., D. Desplanches, H. Hoppeler, E. Caceres, A. Grunenfelder, H. Koubi, M. Leuenberger, B. Sempore, L. Tüscher, and H. Spielvogel. Hormonal and metabolic adjustments during exercise in hypoxia or normoxia in highland natives. *J. Appl. Physiol.* 80(2): 632–637, 1996.—In sea-level natives, exposure to hypoxia for a few weeks is characterized by an increased dependence on blood glucose and a decreased reliance on lactate for energy metabolism during exercise. These metabolic adjustments have been attributed to behavioral changes in the sympathoadrenergic and pancreatic systems. The aim of this study was to test the hypothesis of a reduced sympathoadrenergic activation and subsequent metabolic changes when high-altitude natives are acutely exposed to normoxia. Young Andean natives performed incremental exercise to exhaustion during hypoxia (arterial P_{O_2} 55.1 ± 1.1 Torr) or during acute normoxia (arterial P_{O_2} 78.7 ± 1.7 Torr). As a whole, oxygen uptake was increased in normoxia compared with hypoxia during graded exercise. This finding is not related to a decrease in anaerobic metabolism but rather is interpreted as a consequence of a shift in substrate utilization during exercise (increased contribution of fat as assessed by a reduction in the respiratory exchange ratio). These metabolic changes are not accompanied by modifications of glucoregulatory hormones (catecholamines, insulin, and glucagon). In particular, the exercise-induced catecholamine secretion was similar in chronic hypoxia and acute normoxia. As a consequence, blood lactate accumulation during incremental exercise was similar in both conditions. It is concluded that high-altitude natives do not display any sign of a greater sympathoadrenergic activation during chronic hypoxia and that the exercise-induced hormonal changes remained unaffected by acute inhalation of a normoxic gas mixture.

autonomic nervous system; carbohydrate and fat metabolism; epinephrine; lactate; norepinephrine; pulmonary gas exchange

THE HORMONAL AND METABOLIC ADAPTATIONS to exercise in sea-level natives have been widely investigated during the last 30 yr (11, 18). In response to hypoxia, there is some evidence for an enhanced activation of the sympathoadrenergic system (4, 8, 22, 27) and an increased plasma insulin level (29, 30). These hypoxia-induced hormonal changes have been considered to be responsible for an increased dependence on blood glucose (4) and a decreased reliance on lactate (5) and muscle glycogen (28) during exercise after altitude acclimatization. The exercise-induced catecholamine response is clearly dependent on ambient oxygenation (8, 22, 27) but is also dependent on the duration of exposure to changes in O_2 tension. In this respect, Mazzeo et al. (22) have recently shown that there is a dissociation between norepinephrine (NE), an indicator of sympathetic neural activity, and epinephrine (Epi), an indicator of adrenal medullary response. Thus, during exercise, Epi secretion increased with acute hypoxia and tended to return to a normoxic level after prolonged altitude exposure. By contrast, neural spillover of NE appeared to increase only with chronic exposure to hypoxia. To our knowledge, however, there are no comprehensive data on metabolic and hormonal responses to exercise in subjects fully adapted to altitude, such as highland natives, whether exercising in chronic hypoxia or in acute normoxia.

On the basis of recent data obtained by Mazzeo et al. (22) after 3 wk of acclimatization to 4,300 m, it can be hypothesized that a prolonged sojourn at altitude should be characterized by a sustained sympathetic neural response (as evidenced by a higher level of plasma NE) and a moderate adrenal activation (as reflected by the slight increase of plasma Epi compared with normoxia). If such sympathoadrenergic adaptations occur in highland natives, one could thus expect that, by switching from chronic hypoxia to acute normoxia, these subjects should display a reduced NE response during exercise (and, consequently, a decreased dependence on blood glucose) and a lower plasma concentration of Epi (and, consequently, a reduction in blood lactate accumulation). This hypothesis is supported by the fast changes (within minutes) of the exercise-induced sympathoadrenergic response to exercise when subjects are switched from breathing air to either hypoxia (8) or hyperoxia (7).

The purpose of this study was to assess, in highland natives, the metabolic regulation in relation to sympathochromaffin activation and changes in pancreatic hormone secretion during incremental exercise leading to exhaustion in either chronic hypoxia or acute normoxia.

METHODS

Subjects. Thirty male volunteer subjects (age 24.2 ± 0.5 yr, weight 61.1 ± 1.3 kg, height 168 ± 1 cm) residing at altitude (3,600 m, La Paz, Bolivia) were recruited for the study. All were lifelong highland residents, descendant of a population that has lived at altitude for generations. No specific tests for ethnic background were used in this study, but it is reasonable to presume that most of the subjects were Mestizos, i.e., a mixture of Indian (Aymara and Quechua) and Spanish ancestry. All volunteers had not stayed at low altitude for at least 3 yr before the investigation. The group was homogeneous in terms of fitness as judged by the maximal O_2 uptake ($\dot{V}O_{2max}$)

normalized to body weight, and none of them was in training as an athlete (9). Their weekly exercising time averaged 4.0 ± 0.5 h, with two subjects reporting no physical activity at all. For another study, the subjects had been engaged in an endurance-training program according to methods published elsewhere in detail (9). Briefly, they exercised on a cycle ergometer 5 times/wk, 0.5 h at ~70% of $\dot{V}O_{2max}$, for a total duration of 6 wk. The experiments described below were conducted during the fifth week of the training protocol. All subjects signed an informed consent form. The subjects were divided into two groups approximately matched for $\dot{V}O_{2max}$. The first group was designated as the hypoxic group, whereas the other was referred as to the normoxic group.

At altitude, the subjects completed $\dot{V}O_{2max}$ testing as previously described (9). The hypoxic subjects performed their maximal test while breathing the ambient air (inspired P_{O_2} ~100 Torr), whereas the normoxic subjects were exercised while inhaling a gas mixture recreating the O_2 pressure prevailing at sea level (inspired P_{O_2} ~150 Torr).

$\dot{V}O_{2max}$ during leg-cycling exercise was determined on an electronically braked cycle ergometer (Ergoline) with 30-W increments at 4-min intervals (9).

Blood sampling. Blood samples were withdrawn from a catheter placed in an antecubital vein 15–20 min before exercise. Blood samples were taken at rest and during each workload up to the maximum. Samples were drawn anaerobically over 15 s and were immediately placed in tubes containing stop solutions. From each blood sample, a 0.5-ml aliquot was deproteinized by adding 1.0 ml of ice-cold 10% $HClO_4$. The acid extract was separated by centrifugation and neutralized with KOH. Two milliliters of blood were collected in EDTA for catecholamine, glucose, and free fatty acid (FFA) determinations. Blood samples (2 ml) for analysis of insulin and glucagon were collected in EDTA with a protease inhibitor, apoprotinin (Sigma Chemical). The hormonal and metabolic analyses were performed in Lyon, France.

In addition, blood samples were taken from a fingertip at rest and during various levels of exercise for measurement of lactate (Yellow Springs Instruments lactate analyzer) and P_{O_2}, P_{CO_2}, and pH (Ciba Corning model 280). The instrument was calibrated with standards of known concentrations. Blood arterialization was achieved by inducing hyperemia with an ointment (Trafuril, Ciba Geigy).

Analytic methods. Plasma glucose concentration was determined with a Boerhinger kit (Meylan, France). FFAs were determined by the acyl CoA synthase-acyl oxidase method with a kit (nonesterified fatty acids test, Biolyon). Glycerol concentration was evaluated by an enzymatic method (Boerhinger).

Epi and NE were assayed by high-performance liquid chromatography with electrochemical detection (model LC4B, Biological Analysis System, West Lafayette, IN). Five hundred microliters of plasma were added to 250 µl of 13 mM $Na_2S_2O_5$, 2 ng of dihydroxybenzylamine (internal standard), 250 µl of 2 M tris(hydroxymethyl)aminomethane·HCl buffer (pH 8.6) containing 1% EDTA and 20 mg of acid-washed alumina. This mixture was stirred for 15 min. After the supernatant was decanted, the alumina was washed three times with 1 ml of 20 mM tris(hydroxymethyl)aminomethane·HCl buffer (pH 8.0) containing 0.1% EDTA. After centrifugation, the supernatant was removed. The catecholamines (Epi, NE, and dihydroxybenzylamine) fixed on the alumina were eluted with 90 µl of 0.22 M acetic acid, 0.15 mM sodium metabisulfite, and 0.025% EDTA in an Eppendorf tube and shaken and filtered through a Millipore Millex HV4 filter (Yonesana, Japan). A 40-µl sample of the extract was injected into a reverse-phase analytic column (5 µm, 150 × 4.6 mm; ODS2, Spherisorb) of a Kontron high-performance liquid chromatography system 400 (Zurich, Switzerland). The mobile phase consisted of 27 mM citric acid, 50 mM sodium acetate, 17 mM sodium hydroxide, 1 mM EDTA, 1 mM octylsulfonate, and 9.5% methanol. The flow rate of the mobile phase was fixed at 1 ml/min. Plasma insulin (CIS Biointernational, Gif sur Yvette, France) and glucagon (Pharmacia France, Saint Quentin Yvelines, France) were determined by radioimmunoassay with standard kits.

Statistical analysis. Because not all of the subjects performed the same number of work levels, we only took into account the four levels of exercise that were performed by all of the subjects. Statistical comparisons between groups were calculated with two-way analysis of variance (Statview 4.02, Abacus Concepts, Berkeley, CA). Fisher's protected least significant difference for multiple comparisons was used post hoc when significant F ratios were obtained, and significance was accepted at the $P < 0.05$ level. Data are expressed as means ± SE.

RESULTS

The hematologic, blood gas, hormonal, and metabolic data measured at rest in chronic hypoxia and acute normoxia are reported in Table 1. Inhalation of a normoxic gas mixture resulted in a significant increase in arterial oxygenation (increases in arterial P_{O_2} and arterial O_2 saturation) without changes in arterial P_{CO_2} and pH. The respiratory gas exchange ratio (RER) was significantly lower in normoxic than in hypoxic conditions. Otherwise, circulating concentrations of substrates and key hormones at rest remained unaltered by inhalation of the normoxic gas mixture.

Maximal exercise in acute normoxia was characterized by a significant increase in O_2 uptake (~9%) and a decrease in ventilation and RER (Table 2). The exercise-induced changes in plasma catecholamines, insulin,

Table 1. *Anthropometric parameters, blood gases, hormones, and plasma metabolites measured at rest in chronic hypoxia and acute normoxia*

	Hypoxia	Normoxia
BMI, kg/m^2	22.4 ± 0.6	21.2 ± 0.5
Hb, g/dl	17.4 ± 0.6	17.4 ± 0.3
Hct, %	51.1 ± 1.8	51.1 ± 1.0
Sa_{O_2}, %	94.7 ± 0.8	98.8 ± 0.4*
Pa_{O_2}, Torr	55.1 ± 1.1	78.7 ± 1.7*
Pa_{CO_2}, Torr	28.8 ± 0.5	29.6 ± 0.5
pH	7.42 ± 0.01	7.40 ± 0.00*
HCO_3^-, mM	18.6 ± 0.3	18.3 ± 0.3
NE, pg/ml	546 ± 37	616 ± 50
Epi, pg/ml	280 ± 56	311 ± 54
Insulin, µU/ml	12.4 ± 2.1	11.5 ± 1.5
Glucagon, pg/ml	131.7 ± 24.3	115.3 ± 6.7
Glucose, mM	4.5 ± 0.3	4.3 ± 0.2
Lactate, mM	1.3 ± 0.1	1.3 ± 0.1
FFA, mM	0.283 ± 0.061	0.287 ± 0.055
Glycerol, µM	60.5 ± 5.1	63.3 ± 7.3
β-OH, µM	116 ± 14	156 ± 24
RER	0.91 ± 0.02	0.79 ± 0.03*

Values are means ± SE. BMI, body mass index; Hb, hemoglobin concentration; Hct, hematocrit; Sa_{O_2}, arterial O_2 saturation; Pa_{O_2}, arterial P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; HCO_3^-, bicarbonate concentration; NE, norepinephrine; Epi, epinephrine; FFA, free fatty acids; β-OH, β-hydroxybutyrate; RER, respiratory exchange ratio. *Significantly different from hypoxia ($P < 0.05$).

Table 2. *Cardiorespiratory parameters, blood gases, hormones, and plasma metabolites measured at exhaustion in chronic hypoxia and acute normoxia*

	Hypoxia	Normoxia
$\dot{V}O_2$, ml·min^{-1}·kg^{-1}	45.6 ± 1.3†	48.6 ± 1.4†
$\dot{V}E$, l/min	140.6 ± 6.3†	109.4 ± 6.6*†
RER	1.12 ± 0.02†	1.01 ± 0.02*†
HR, beats/min	189 ± 3†	184 ± 3†
NE, pg/ml	3,672 ± 519†	3,622 ± 445†
Epi, pg/ml	1,068 ± 184†	994 ± 132†
Insulin, μU/ml	5.2 ± 0.7†	4.3 ± 0.4†
Glucagon, pg/ml	124.1 ± 20.2	140.6 ± 10.9†
Glucose, mM	4.5 ± 0.2	4.2 ± 0.2
Lactate, mM	8.7 ± 0.5†	8.6 ± 0.3†
FFA, mM	0.184 ± 0.025	0.160 ± 0.022†
Glycerol, μM	85.5 ± 11.7†	86.0 ± 8.0†
β-OH, μM	489 ± 44†	568 ± 44†

Values are means ± SE. $\dot{V}O_2$, oxygen uptake; $\dot{V}E$, minute ventilation; HR, heart rate. *Significantly different from hypoxia. †Significantly different from resting values.

and glucagon were similar in both chronic hypoxia and acute normoxia. Although plasma levels of glycerol and β-hydroxybutyrate increased during maximal exercise, the level of circulating FFAs was reduced by exercise in both hypoxia and normoxia.

The cardiorespiratory, hormonal, and metabolic responses during the incremental exercise to exhaustion are summarized in Figs. 1–4. There was a significant effect of O_2 availability on O_2 uptake, ventilation, and RER (Fig. 1). In contrast, the kinetics of the glucoregulatory hormones (Fig. 2) and plasma metabolites (Figs. 3 and 4) were superimposable in chronic hypoxia and acute normoxia.

DISCUSSION

Exposure to high altitude (>3,000 m) for a few weeks has been reported to result, during exercise, in an increased dependence on blood glucose as a fuel (4) and

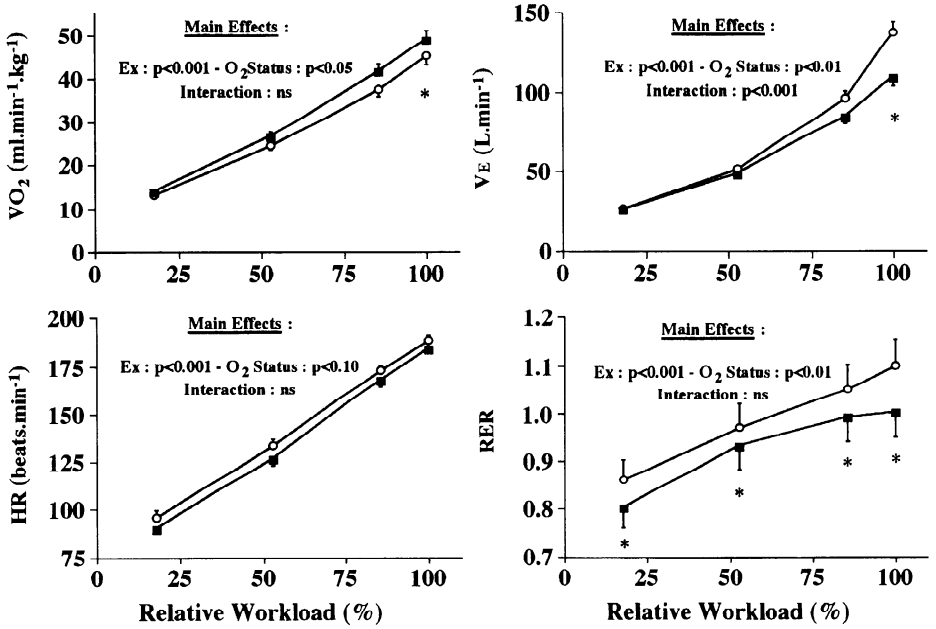

Fig. 1. Oxygen uptake ($\dot{V}O_2$), minute ventilation ($\dot{V}E$), heart rate (HR), and respiratory exchange ratio (RER) as a function of exercise (Ex) intensity expressed as percentage of maximal aerobic power output (%P_{max}) under hypoxic (○) and normoxic (■) conditions. Values are means ± SE. *Significantly different from hypoxia at same relative exercise intensity. ns, Not significant.

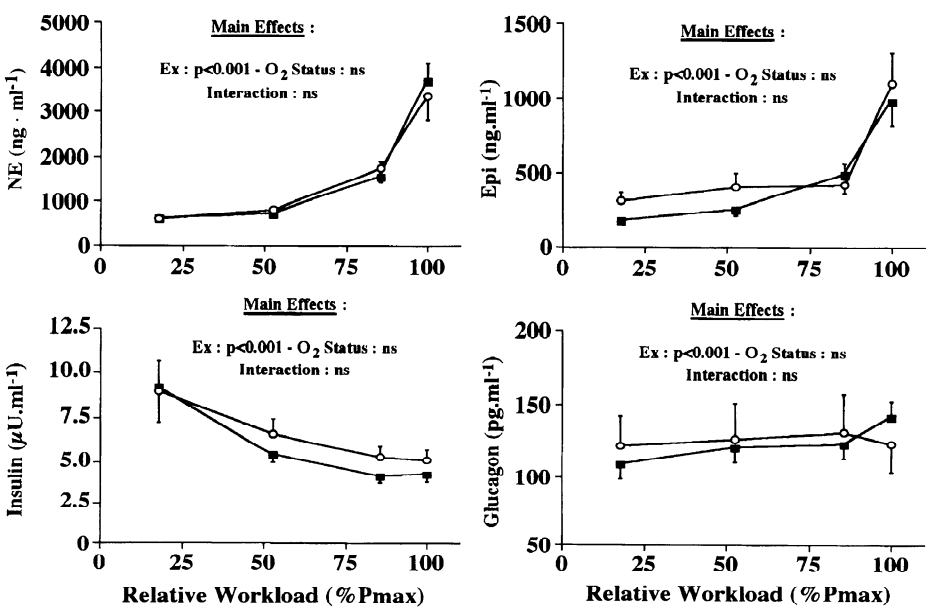

Fig. 2. Plasma norepinephrine (NE), epinephrine (Epi), insulin, and glucagon concentrations as a function of exercise intensity expressed as %P_{max} under hypoxic (○) and normoxic (■) conditions. Values are means ± SE.

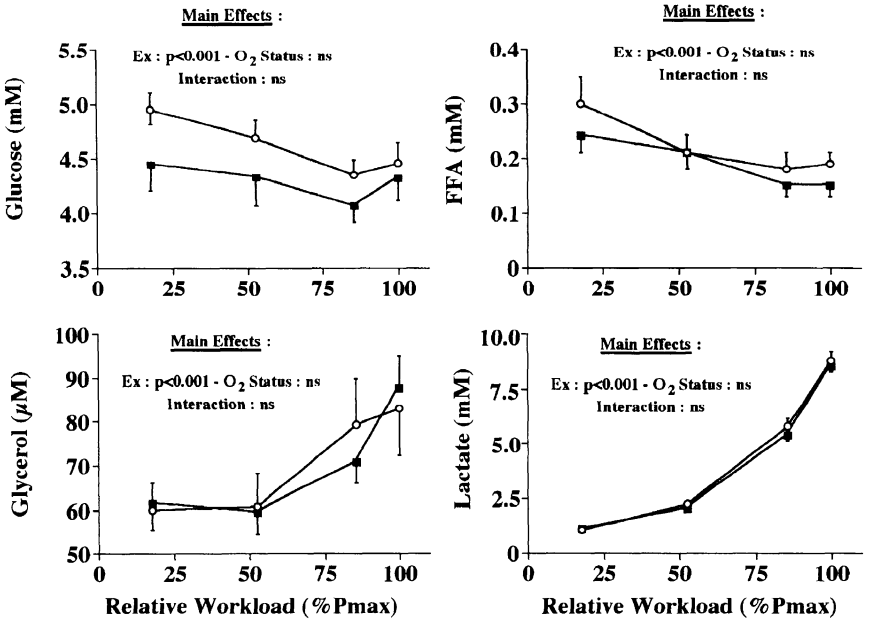

Fig. 3. Plasma glucose, free fatty acid (FFA), glycerol, and lactate concentrations as a function of exercise intensity expressed as $\%P_{max}$ under hypoxic (○) and normoxic (■) conditions. Values are means ± SE.

a decreased reliance on lactate (5) and muscle glycogen (28), with an apparent increase in FFA mobilization (16, 17) and utilization (16). These metabolic changes are hormonally regulated, mainly by catecholamines (4, 22) and insulin (29, 30). However, altitude acclimatization is a slow process and requires several weeks or months to reach full expression (3), and, to our knowledge, there is no comprehensive study on the metabolic and hormonal responses to exercise in highland natives whether exercising in chronic hypoxia or in acute normoxia.

However, several factors influence the hormonal and metabolic responses during exercise, including diet and training status of the subjects. Unfortunately, we did not monitor the nutritional intake of our subjects, but they were asked to maintain their dietary habits throughout the entire period of the studies. However, the body mass index [BMI; weight (kg)/height (m^2)] has been shown to be a relatively good measure of nutritional status (10). Before the training program in which all the subjects were engaged (9), the BMI averaged 21.7 ± 0.4 kg/m^2 and remained stable (21.6 ± 0.4 kg/m^2) up to the end of the training study (9). On the other hand, the BMI was similar in the two groups of subjects exercised either in chronic hypoxia or in acute normoxia (Table 1). From the BMI data, it appeared that our subjects were within the normal range of anthropometric standards (10). In addition, it was recently reported that the nutritional intake of young Bolivians is influenced by socioeconomic status and not by altitude (24). Our subjects were postgraduate students of high socioeconomic status and therefore can be considered as adequately nourished.

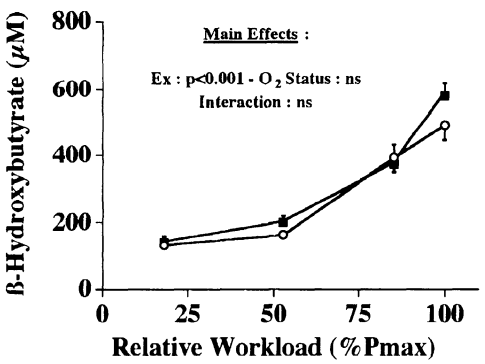

Fig. 4. Plasma β-hydroxybutyrate concentration as a function of exercise intensity expressed as $\%P_{max}$ under hypoxic (○) and normoxic (■) conditions.

Before training, all but two subjects were physically active, with a mean recreational activity of 4 ± 0.5 h/wk. During the training period, they were asked to maintain their exercising habits. It is well known that training influences the sympathoadrenergic response to exercise (11, 18, 19), but it was shown (18) that training increases the responsiveness of the sympathoadrenergic system. We can thus hypothesize that examining the subjects after 5 wk of training should not represent a major problem for data interpretation.

Recently, it was reported that high-altitude natives displayed a preferential use of carbohydrate as fuel for muscle work (12). During incremental exercise, we found that, for a given work, the RER was decreased in acute normoxia compared with chronic hypoxia (Fig. 1), suggesting, for highlanders, a greater reliance on fat during exercise in acute normoxia. One must recognize the limitation of using the pulmonary-based measurement of the RER to reflect metabolism. Indeed, hyperventilation and disturbances in acid-base balance can create artifacts in the RER. However, in the present study, exercising in acute normoxia was characterized by a lower ventilatory output (Fig. 1) and by a similar blood lactate accumulation (Fig. 3), and the mean RER was always lower in acute normoxia rather than varying randomly (Fig. 1). That fat metabolism was enhanced during exercise in normoxia is somewhat supported by the significant effect of normoxia on O_2 uptake during graded exercise (Fig. 1), and this observation has been previously noted by some authors (15). Indeed, there are some reports showing that oxidation

of FFAs is accompanied by a higher O_2 consumption than is carbohydrate oxidation (14). Thus our data, although limited, do suggest that exercising in normoxia for high-altitude natives resulted in an enhanced fat utilization. To clarify this issue, it would have been necessary to determine plasma FFA turnover and oxidation by stable isotope infusion (20) and to take muscle biopsies before and after exercise to appreciate muscle triglyceride utilization (13).

On the other hand, it has been shown that glucose utilization is correlated with arterial NE concentration (4, 22), which increases as exposure to high altitude is prolonged. On the basis of the fact that glucose metabolism and sympathoadrenal activation can be affected within minutes by the O_2 concentration of the inspired gas (7, 8), one can thus expect that exposure of high-altitude natives to acute normoxia should result in a decreased level of plasma NE during exercise. However, at rest (Table 1) as well as during exercise (Table 2, Fig. 2), plasma NE was similar in chronic hypoxia and acute normoxia. Our inability to demonstrate a lower NE level in acute normoxia might be that plasma levels of catecholamines may not reflect sympathetic nerve activity (27). It is generally considered that the sympathetic nervous system is stimulated by two primary signals associated with voluntary exercise, i.e., central command and chemosensitive afferent feedback from the contracting skeletal muscles (25). Because the main stimulus for muscle sympathetic activity during exercise is governed to a large extent by O_2 delivery to active muscles (27) and because O_2 delivery to the exercising limb is not different in chronic hypoxia and acute normoxia (2), the muscle chemoreflex drive might have been the same under our conditions, and similar increases in plasma NE occurred in chronic hypoxia and acute normoxia.

Recently, Mazzeo et al. (22) demonstrated that Epi, a marker of adrenal medullary activity, was significantly elevated with acute altitude exposure and tended to return to a normoxic level with altitude acclimatization (4). In addition, a strong association among exercise blood lactate concentration, lactate turnover, and Epi response has been demonstrated (22). It is not known, however, whether, during lifelong altitude residence, adrenal medullary activation by hypoxia subsides or remains elevated compared with sea level. In the former case, unchanged exercise-induced Epi and lactate kinetics could be expected in response to exercise in acute normoxia, whereas in the latter both a decreased plasma Epi and lactate concentration should occur. The present study provided evidence that, in high-altitude natives, the exercise-induced adrenal medullary activation was similar in chronic hypoxia and acute normoxia (Fig. 2), and blood lactate kinetics were superimposable in both conditions (Fig. 3). This would suggest that the slight adrenal activation of sea-level natives consecutive to prolonged exposure to hypoxia (4, 22) vanishes when the altitude sojourn is prolonged over years, as in our highlanders. Therefore, it is not surprising to notice that blood lactate accumulation during incremental exercise was similar in chronic hypoxia and acute normoxia (Fig. 3).

In recent years, it was shown that, both at rest and during exercise, the plasma insulin level was increased by acute exposure to hypoxia (4, 29, 30), but divergent results were obtained after altitude acclimatization. Thus, after 3 wk of exposure to 4,300 m, Brooks et al. (4) reported a normalization of insulin secretion, whereas Young et al. (29, 30) reported a higher plasma insulin concentration at rest as well as during exercise after prolonged exposure to increasing altitude. Our results showed that our high-altitude natives displayed a resting mean plasma insulin level (Table 1) similar to that obtained in altitude-acclimatized sea-level natives (4, 29, 30). In response to incremental exercise, whether in chronic hypoxia or acute normoxia, plasma insulin displayed a gradual decrease to reach ~5 μU/ml at exhaustion (Fig. 2). Although the influence of prolonged exposure to hypoxia on insulin secretion during exercise in sea-level natives remains to be determined, our data provide evidence that the level of pancreatic hormones in high-altitude natives is within the normal range and is not affected by acute exposure to normoxia.

With respect to plasma metabolites (glucose, FFAs, and glycerol), we found that the exercise-induced changes were similar in chronic hypoxia and acute normoxia (Fig. 3). It needs, however, to be mentioned that lipid oxidation by the liver (as assessed by β-hydroxybutyrate concentration) was increased during exercise in hypoxia as well as in normoxia (Fig. 4). It is generally believed that the concentration of ketone bodies in the blood does not increase during exercise but rises sharply in the postexercise period (21). Subsequently, Adams and Koeslag (1) provided evidence for a close relationship between ketosis and liver glycogen concentration. It can thus be hypothesized that the glycogen content of our high-altitude natives was low, resulting in an immediate increase in blood β-hydroxybutyrate during exercise (Fig. 4). This assumption of low hepatic glycogen stores in highlanders remains to be proven, but it was shown that adult rats exposed to 3,800 m for 2 mo displayed a significantly lower glycogen content (6). The increase in β-hydroxybutyrate observed in the present study might be particularly important in providing substrates in a substantial amount (~0.5 mM) for the exercising muscles. Furthermore, there is now evidence that the use of ketone bodies by many tissues including muscle reduces glucose utilization (23).

It must be kept in mind, however, that there are other counterregulatory hormones (e.g., cortisol and growth hormone) that are implicated in the metabolic response to exercise and are affected by hypoxia (26). Whether these hormones played a role in the changes in fuel utilization reported in the present study remains, however, to be evaluated.

In conclusion, this study demonstrates that, in high-altitude natives, there is no evidence of a sympathoadrenergic activation as a consequence of chronic exposure to hypoxia. Furthermore, during acute exposure to

normoxia, the exercise-induced hormonal responses were similar to those observed during exercise in chronic hypoxia, and blood lactate accumulation during incremental exercise was similar in both conditions.

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