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Physical Exercise at Altitude – Acclimation and Adaptation Effects in Highlanders on Different Continents

Muskelarbeit in der Höhe – Akklimatisierung und Adaptation bei Hochlandbewohnern auf verschiedenen Erdteilen

REVIEW

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Summary

› **In altitude populations** acclimatization (physiological changes during sojourn) and adaptation (genetic variation) are important for survival and performance capacity. Here we compare physiological differences during exercise in highlanders in South America, Asia (Tibet and Nepal) and East Africa (Ethiopia and Kenya).

› **During** short-lasting activities, the reduced air friction is an advantage. During longer exercise duration, the reduced maximal aerobic metabolism is limiting. During submaximal exercise, various compensatory mechanisms are effective: increased ventilation, reduction of respiratory alkalosis by the kidneys, growth of the lungs during childhood with improved diffusion capacity, rise of hemoglobin mass and concentration (only in America), changes in hemoglobin-oxygen affinity, reduction of muscle fiber magnitude shortening the distance for O_2 diffusion, reduction of mitochondrial volume corresponding to the lowered O_2 consumption.

› **There are genetic differences** in populations living longer at altitude than South Americans. In Tibetans hemoglobin concentration does not rise up to 4000m (reduction of the effect of Hypoxia Inducible Factor 2), while more nitric oxide facilitates ventilation and perfusion. In some of the Ethiopians, arterial O_2 saturation is astonishingly high; an increased oxygen affinity of hemoglobin might be the cause. The high exercise capacity of Ethiopians and Kenyans living between 2200 and 2900m seems not to be mainly an altitude effect, but the result of intense physical training since childhood and of biomechanical factors (e. g. mass and length of legs).

KEY WORDS:
Hypoxia, Physical Training, Genetics

Zusammenfassung

› **Bei Höhenbewohnern** sind Akklimatisierung (physiologische Änderungen während eines Aufenthalts) und Adaptation (genetische Variation) wichtig für Überleben und Leistungsfähigkeit. Hier vergleichen wir physiologische Unterschiede während Arbeit bei Höhenbewohnern in Südamerika, Asien (Tibet und Nepal) und Ostafrika (Äthiopien und Kenia).

› **Während** kurzdauernden Aktivitäten ist die verringerte Luftreibung von Vorteil. Während längerer Belastungen ist der erniedrigte maximale aerobe Stoffwechsel begrenzend. Während submaximaler Leistung werden verschiedene Kompensationsmechanismen wirksam: vermehrte Atmung, Verringerung der respiratorischen Alkalose durch die Nieren, Wachstum der Lungen in der Kindheit mit verbesserter Diffusionskapazität, Erhöhung der Hämoglobinmasse und -konzentration, Änderungen der Hämoglobin-Sauerstoffaffinität, Verkleinerung der Muskelfasern und damit Verkürzung der Diffusionsstrecke für O_2, Verringerung des Mitochondrienvolumens entsprechend dem verringerten O_2-Verbrauch.

› **Es gibt genetische Unterschiede** zu Südamerikanern bei länger in Höhe lebenden Gruppen. Bei Tibetern steigt die Hb-Konzentration bis auf 4000m nicht (Verringerung der Wirkung des Hypoxie-Induzierbaren Faktors 2), während mehr Stickoxid Atmung und Kreislauf erleichtert. Bei einem Teil der Äthiopier ist die arterielle O_2-Sättigung erstaunlich hoch; eine vergrößerte Sauerstoffaffinität des Hämoglobins könnte die Ursache sein. Die vergrößerte Leistungsfähigkeit von zwischen 2200 und 2900m lebenden Äthiopiern und Kenianern scheint nicht ein Ergebnis der Höhenwirkung zu sein, sondern von intensivem Training seit der Kindheit und biomechanischen Faktoren (z. B. Masse und Länge der Beine).

SCHLÜSSELWÖRTER:
Hypoxie, körperliches Training, Genetik

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Introduction

High altitudes above 2000 m are not the original habitat of man. Therefore low barometric pressures with the concomitant fall in oxygen pressure (1/2 at 5500m above sea level), reduced temperature (-6°/1000m) and increases in radiation (light, cosmic rays) challenge physiological functions. Short sojourns without artificial O_2 supply are possible up to 8848m as firstly shown by Messner and Habeler (56).

But reduction of maximal oxygen uptake during acute exposure begins already at 800m above sea level and is more marked in trained subjects (22). Organisms react by three mechanisms: acute reaction (seconds to hours), acclimation (compensatory physiological changes, days to years) and adaptation (genetic changes). In highlanders acclimation (e. g. growth of thorax in childhood) as well as adaptation play a role. There is only one advantageous environmental change: the reduction in air resistance allows improvements in jumping, throwing, short distance running and cycling (19, 29).

Complete adaptation needs thousands of years. There are 3 regions with long-term inhabitants above 2500m: South America and Asia (Tibet and Nepal) up to 5000m, Africa (Ethiopia and Kenya) up to ›

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4000m. Humans entered America approximately 20 000 years ago and reached the high plateaus in South America 10 000 years later; human relicts in Tibet date back 20 000 to 40 000 years (5). First proofs for the presence of Homo sapiens in Ethiopia originated 200 000 years ago (35). The situation is complicated by later immigration of people from low altitude. But there remained the selective pressure for genes favorable for life and reproduction in hypoxia now distributed in the mixed population.

The crucial problem at altitude is the supply of oxygen. There are 3 strategies to reduce this problem: improvement of O_2-transport, reduction of consumption, reduction of minimal O_2 pressure necessary for enzyme function.

In the following we will analyze the steps of O_2-transport. The amount of O_2 is always equal to total oxygen consumption ($\dot{V}O_2$). Bold characters signify decisive factors of defense against hypoxia:

$\dot{V}O_2 = \mathbf{\dot{V}_E} * (F_IO_2 - F_EO_2)$
$\dot{V}_E$ expiratory ventilation, F fraction of gas

$\dot{V}O_2 = \mathbf{D_{pul}} * (PO_{2A} - PO_{2cap})$
D_{pul} pulmonary diffusion capacity, A alveolar, cap capillary

$\dot{V}O_2 = \mathbf{Q} * (\mathbf{CO_{2a}} - CO_{2v})$
Q cardiac output, C content in blood, a arterial, v mixed venous

$\dot{V}O_2 = \mathbf{D_{tissue}} * (\mathbf{PO_{2cap}} - PO_{2mito})$
cap capillary, mito mitochondrial

Ventilation

$\dot{V}O_2 = \mathbf{\dot{V}_E} * (F_IO_2 - F_EO_2)$

To get an impression of the importance of ventilation we may consider the effect of an acute rise to 5500 m of altitude. Atmospheric pressure falls to half, therefore the oxygen content in 1 l inspired air is only 50% of that at sea level. To transport an equal amount of O_2 as at sea level to the alveoli the ventilation should be doubled. This is impossible during maximal exercise thus leading to an unevitable reduction of $\dot{V}O_2$max.

This effect was demonstrated in acute hypoxia corresponding to 4000 m of altitude (48). Maximal ventilation was approximately equal as in normoxia for BTPS (body temperature and pressure, saturated) conditions (120 l/min), but reduced from 100 to 55 l/min for STPD (standard temperature and pressure, dry), the decisive condition for metabolism (50). Consequently the alveolar PO_2 falls markedly. Ventilation may compensate this drawback only during submaximal exercise.

The ventilation is stimulated by hypoxia and hypercapnia. The sensitivity to these stimuli rises with time in sojourners. The following compensatory mechanisms are helpful in highlanders. Growth of thorax and lung volume are especially stimulated during childhood and adolescence in altitude populations. Later only training of respiratory muscles is effective. In Tibetans enlarged diameters of bronchioli caused by nitric monoxide (NO) facilitate the ventilation (5); additionally their hypoxic ventilatory response is larger than in Andeans (14). Also a reduction of respiratory rate possible by increased tidal volume has a positive effect: relatively more fresh air reaches the alveoli during one inspiration. Interestingly, Tibetans ventilate less than acclimatized Han during exercise because of improved mechanical conditions as well as the high diffusion capacity described in the next paragraph (60).

Diffusion in the Lungs

$\dot{V}O_2 = \mathbf{D_{pul}} * (PO_{2A} - PO_{2cap})$ $D_{pul} = K * (\text{Area/Distance})$
K diffusion coefficient

Compared to sea level conditions the difference PO_{2A} - PO_{2cap} is reduced because of the low PO_{2A}. A possible compensatory mechanism is a more rapid blood flow lowering endcapillary PO_2 and thus stabilizing oxygen diffusion. This might be caused by the increased cardiac output in Tibetans and Ethiopians (25, 26). In spite of this, however, A-aDO2 during exercise was lower in Tibetans than in acclimatized Han explainable by the high diffusion capacity of their enlarged lungs (60).

The area of erythrocytes as another diffusion-enhancing factor is typically increased by their enlarged number in highlanders in America. In Tibet and Ethiopea this effect is smaller or even lacking (see below).

Blood

$\dot{V}O_2 = Q * (\mathbf{CO_{2a}} - \mathbf{CO_{2v}})$

Hemoglobin concentration and Hemoglobin-Oxygen affinity are two decisive factors for oxygen transport in blood.

Hemoglobin concentration. The "typical" increase of hemoglobin concentration [Hb] at altitude follows from an initial reduction of plasma volume and a subsequent increase of Hb mass (14, 56). It is, however, regularly observed only in sojourners and in residents in North and South America; Weil et al. (55) measured a threshold at an alveolar PO_2 of approximately 70 mmHg in males living at least 2 years at altitude in Colorado. A pathological increase of red cell mass (chronic mountain sickness or Monges disease) is occasionally observed in males living above 2500m. A useful counteradaptation is a lack of genes for high fibrinogen concentration in Quechua reducing the danger of thrombosis (42). The most important regulator of red cell production is erythropoietin (Epo) (28). No marked differences in [Epo] have been observed in blood sampled during day time between sea level and altitude inhabitants (9, 13, 47, 48). But [Epo] is increased during the night following phases of low SO_2 at 2600m of altitude, whereas at sea level variations are smaller or lacking (18, 23, 32). Physical training increases the Hb mass but decreases [Hb] because of a concomitant increase in plasma volume in South American highlanders equally as in lowlanders (13, 47, 53).

In Tibetans an increased [Hb] is not observed up to 4000m in spite of a rather low arterial SO_2 (4, 5, 59). Wagner et al. (54) detected that maximal oxygen uptake is even negatively correlated to [Hb] at 4200m. In Ethiopia Beall et al. (8) measured [Hb] at 3540m of altitude like in sea level subjects (Table 1). Cheong et al (15) could confirm this in the Amhara population but not in the Omoro. Interestingly a nutrition rich in nitrate as observed in the former might also reduce Epo secretion (2, 15).

Astonishingly, no measurements of Hb mass or blood volume in Tibet and Ethiopia seem to exist. Measurements have been performed only in Kenyan runners (living at approx. 2100m) after travelling to Germany (41). The Hb mass per kg was initially equal to that in German runners, but decreased by 5% during 6 weeks in the lowland without change in absolute $\dot{V}O_2$max.

Possibly measurements of plasma volume in Ethiopians and Peruvians might explain the lacking increase in [Hb] in the former (17). Their plasma volume was high, thus explaining a dilution of Hb in whole blood. The state of physical training has not been communicated; this is unfortunate because training causes a larger rise in plasma than in red cell volume (e. g. 13).

Table 1

Examples of hemoglobin concentration and arterial oxygen saturation in male highlanders. Means±SE. ut=untrained. The training status is not indicated in the last 3 studies; [Hb] tends to slightly lower values in fit subjects.

REGION	ALTITUDE [m]	SUBJECTS	[Hb] [g/dl]	SO_2 [%]	SOURCE
Germany	30	14 ut	15.3±0.2	98.1±0.2	13
Colombia	2600	15 ut	17.4±0.2	93.1±0.2	13
Bolivia	3600	30 ut	17.6±0.3	89.7±0.9	21
Bolivia	3900-4000	283	19.1±0.2	92.0±0.2	6
Tibet	3800-4065	110	15.6±0.2	89.0±0.3	6
Ethiopia	3530	128	15.9±0.1	95.3±0.2	8

Hemoglobin-Oxygen affinity. The sigmoidal oxygen dissociation curve (ODC) results from affinity and cooperativity changes in dependence on loading with O_2. A left shift caused by special hemoglobins like in altitude animals and the human fetus favors oxygen binding (34). In human adults this effect has been observed in twins with a high affinity hemoglobin: their maximal O_2 uptake was even higher at altitude than at sea level (24). In normal man respiratory alkalosis may cause such a left shift. But astonishingly this is compensated in sojourners and South American highlanders by nonrespiratory acidosis and increased 2,3-Biphosphoglycerate concentration (33, 46, 58). Only at extreme altitude above 5000m is hyperventilation strong enough to cause a left shift of the curve (43).

In contrast, left shifts of the ODC have been observed in Asian and African highlanders (15, 39). In Ethiopia this might be the cause of the often observed high SaO_2. Interestingly the concentration of glutathione which causes a left shift of the ODC (37) was markedly increased in Sherpas (39).

However, most measurements were performed on blood equilibrated with varying O_2 pressures after sampling (in vitro). There are observations that in vivo (i. e. the blood is equilibrated with varying O_2 pressures in the body before sampling it) the ODC at altitude is left-shifted in man, too (3). Causes might be the interchange of influencing substances (e. g. chloride, glutamate) with interstitial fluid and tissue cells (reviewed in (10).

When considering arterial O_2 saturation, the marked altitude-dependent decrease in newcomers is partly reversed in acclimatized subjects and native South Americans, the value is astonishingly low in Tibetans and nearly as high as at sea level in many subjects in Ethiopia (4, 15, 26).

Circulation

$$\dot{V}O_2 = \mathbf{Q} * (\mathbf{CO_{2a}} - CO_{2v})$$

Compared to ventilation and blood, changes in circulation play only a minor role for altitude sustainability. Initially cardiac output is increased for each work rate step. With acclimation maximal cardiac output is reduced; causes are increased blood viscosity, pulmonary vasoconstriction and reduction of sympathic stimulation. Maximal heart rate seems to be slighly reduced in Tibetans (38). However, in South American highlanders it is not changed at 3600m (1, 21). Submaximal cardiac output is similar at altitude and sea level in highlanders in South America (52).

At rest and probably also during exercise Tibetans at 4200m compensate for ambient hypoxia with higher pulmonary blood flow and thus O_2 delivery without higher pulmonary arterial pressure (38). This is probably caused by high NO levels reducing the Ca^{++} effects in smooth muscle cells and thus decreasing the resistance in the arterioles (25). Similar effects were observed in Ethiopians at 3700m of altitude (26). As mentioned above, the Amhara ingest a high amount of nitrate, a precursor of NO (2, 15). Another important factor is that an increase of the Hct is only useful up to an optimal value (approximately 53-55%), beyond this value blood viscosity rises markedly (11).

Maximal cardiac output is increased in Tibetans compared to American highlanders (38). Forearm blood flow and the corresponding oxygen delivery rose more than 3 times during exercise compared to lowlanders in the United States (20).

Surprisingly, the number of capillaries per mm^2 of tissue is not increased in Sherpas compared to lowlanders (30).

Diffusion in Tissues and Metabolism

$$\dot{V}O_2 = \mathbf{D_{tissue}} * (\mathbf{PO_{2cap}} - PO_{2mito})$$

Fiber diameter and volume density of mitochondria in muscles are low in many Caucasian climbers after expeditions as well as in Sherpas (30). Because of the lowered O_2 supply many mitochondria are simply not necessary. Tibetans living at low altitude equally showed low mitochondrial numbers pointing to a genetic cause (31). Interestingly, the right shift of the ODC at moderate altitude supports O_2 diffusion from capillaries to mitochondria.

At altitude there is a shift to carbohydrate combustion which needs less oxygen than fat (reviewed in (12). Because of this fact there are many suggestions of an improved efficiency of metabolism in highlanders. But a critical examination of publications does not support this hypothesis. The relatively low $\dot{V}O_2$max in Kenyans at both high and low altitudes might be related to specific features of their physique (low body mass index, long thin legs, good elastic energy storage). The low energy cost of carrying loads uphill in Sherpas has been partly explained by their motor skills in balancing the loaded upper body (36).

Genetics

There is a large number of genetic studies in highlanders (summarized in (4, 40, 51)). Especially of interest are the hypoxia inducible factors (HIF): HIF-2 influences the production of erythropoietin while HIF-1 stimulates the synthesis of the vascular endothelial growth factor (VEGF) and the expression of glycolytic enzymes.

In Tibetans modifications of a single nucleotid polymorphism (SNP) near the EPAS 1 gene, which encodes HIF-2, hinder the increase of [Hb] at altitude (7). According to Song et al. (49) genetic changes at the Prolyl Hydroxylase Domain protein 2 (PHD2/EGLN1) hinder the production of HIF-2alpha, but stimulate the production of HIF-1alpha leading to increased NO formation. The positive effect is a a reduced severity of chronic mountain disease, the negative effect of low [Hb] ›

on oxygen transport is compensated by the high blood flow. In Sherpas a modified gene for peroxisome proliferator-activated receptor alpha (PPARα), a transcriptional regulator of fatty acid metabolism, reduces the consumption of fatty acids (27).

According to Scheinfeld et al. (45) there is a lot of hypoxia-caused genetic variants in Ethiopia distinct from other high altitude regions, but the effects are partly similar (e. g. low [Hb] as in Tibet).

Apparently epigenetic changes play a role in Andean highlanders: The HIF-2alpha gene (*EPAS1*) is less methylated and thus leads to increased expression of the EPAS1 protein (16).

Considering the successful runners from Kenya and Ethiopia, no special genetic properties have been detected until recently (57).

Conclusions

Considering the physiological adaptations in the different groups of highlanders the time since their immigration to high altitude is of importance for useful genetic changes. The South Americans who arrived as the latest have reacted with increased hemoglobin concentration. The resulting high viscosity impedes blood flow and increases the risk of chronic mountain sickness. Tibetans avoid this but the necessary high blood flow also costs additional energy. In Ethiopa the best adapted groups possibly possess genes from very early immigrants to altitude, their high arterial SO_2 points to high oxygen affinity of Hb.

Anthropological properties and lifelong training are useful during exercise at altitude. At sea level especially Ethiopians and Kenyans from moderate altitude are successful athletes. In other highlanders the gain of performance capacity when descending is less than in lowlanders after altitude training (reviewed by Saunders (44)).

Conflict of Interest

The authors have no conflict of interest

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