REVIEW ARTICLE

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Physiological Effects of Chronic Hypoxia

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THE PHYSIOLOGY OF CHRONIC HYPOXIA ENCOMPASSES AN ENORMOUS field of knowledge. This review concentrates on two areas in which important advances have recently been made. The first is hypoxia-inducible factors (HIFs), which constitute the master switch in the human response to hypoxia. The second is high altitude, causing hypoxia in millions of people. Recent advances in technology show promise for alleviating high-altitude hypoxia.

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HYPOXIA-INDUCIBLE FACTORS

In 1774, Joseph Priestley heated mercuric oxide, and when he studied the gas that was produced, he wrote, "What surprised me more than I can well express, was that a candle burned in this air with a remarkably vigorous flame. . . . I was utterly at a loss to account for it." He added, "From the greater strength and vivacity of the flame of a candle in this pure air, it may be conjectured that it might be peculiarly salutary to the lungs in certain morbid cases."[1] It is sobering that although Priestley first produced oxygen and pondered on its potential nearly 250 years ago, nature coyly kept the secret of the body's coordinated response to hypoxia until just 25 years ago.

The key is the family of HIFs. These are transcription regulators that respond to the prevailing level of oxygen and bind to specific DNA sequences, thus controlling the rate of gene transcription. One of the first clues to the discovery of HIFs and their role was the identification of these factors as proteins that bind to the hypoxia response element (HRE) of the erythropoietin gene under hypoxic conditions.[2]

It subsequently became clear that hypoxia-inducible factor 1 (HIF-1) is a dimer consisting of HIF-1α and HIF-1β subunits. HIF-1β is transcribed continually, but HIF-1α is present at very low levels under normoxic conditions. HIF-1α is normally hydroxylated; in the presence of oxygen, iron, and 2-oxoglutarate, HIF-1α reacts with the von Hippel–Lindau protein and then undergoes ubiquitination and is destroyed.

In hypoxia, the oxygen required for HIF-1α to be ubiquitinated is missing. Thus, HIF-1α persists intact, moves to the nucleus (where it binds with HIF-1β), and recruits coactivator proteins to the HIF binding site with the HRE (Fig. 1). The result is up-regulation of a large number of target genes that aid in the adaptation to hypoxia, including the erythropoietin gene (resulting in the generation of more red cells) and *VEGF* (resulting in the generation of more blood vessels). In addition, some genes are down-regulated, such as *PDK1*, leading to decreased mitochondrial oxygen consumption.

A closely related protein, hypoxia-inducible factor 2α (HIF-2α), was discovered somewhat later. Its processing is similar to that of HIF-1α, but HIF-1α has a very wide distribution, whereas HIF-2α is expressed predominantly in macrophages in normal tissues.

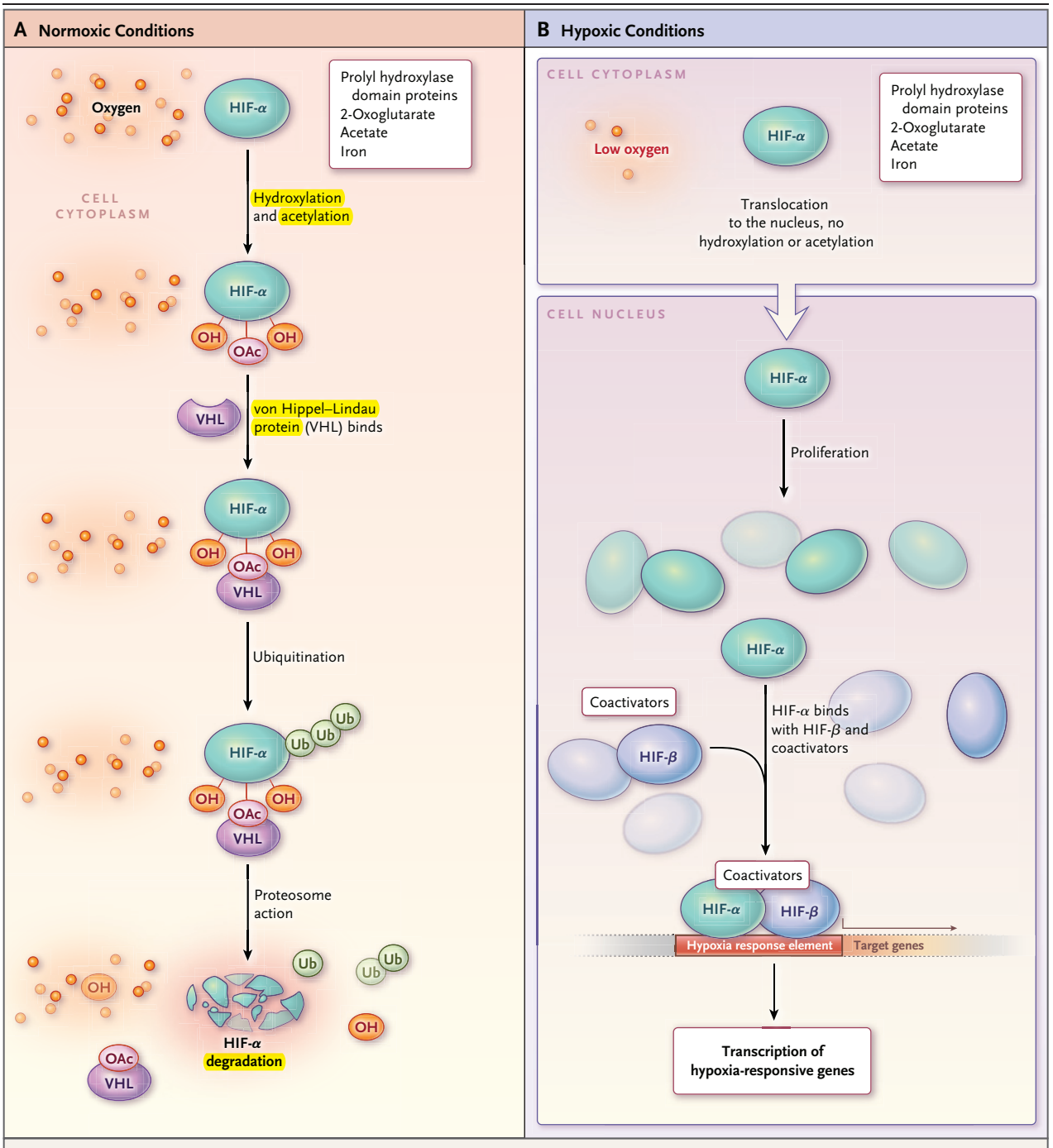

Figure 1. Role of Hypoxia-Inducible Factor α (HIF-α) under Normoxic and Hypoxic Conditions.

Under normoxic conditions, HIF-α is hydroxylated by prolyl hydroxylase domain proteins. It then interacts with von Hippel–Landau (VHL) protein, and with the addition of ubiquitin, proteosomal degradation takes place. Under hypoxic conditions, HIF-α does not undergo degradation but instead translocates to the nucleus, where it binds with HIF-β and then recruits coactivators at the hypoxia response element, initiating gene transcription. OAc denotes acetyl-oxy (acetoxy), and OH hydroxyl.

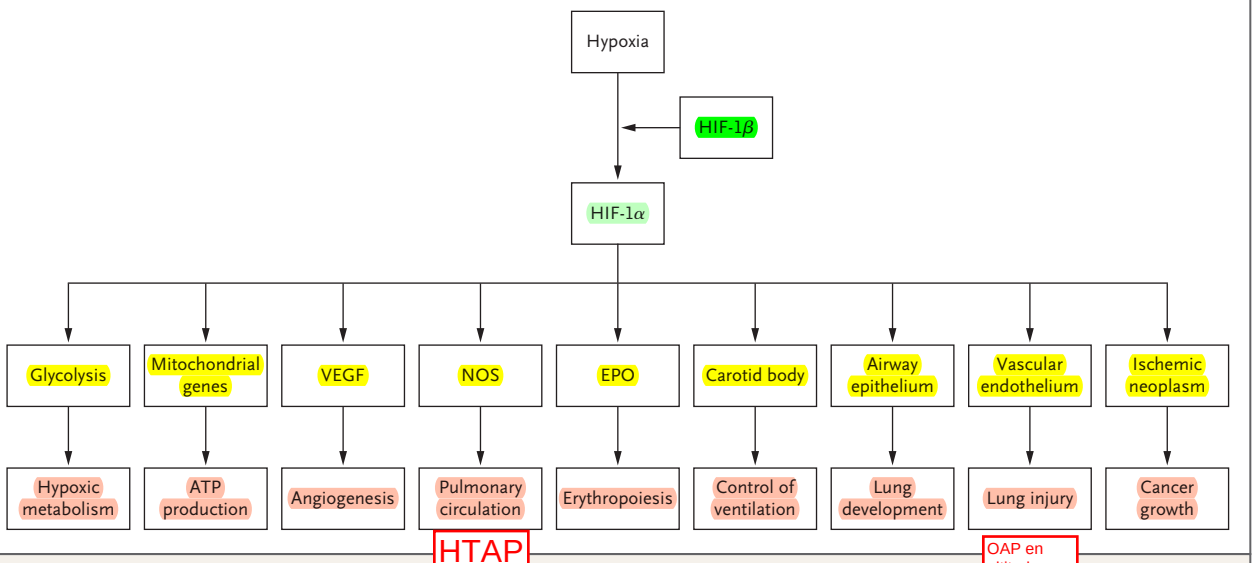

Figure 2. The Spectrum of Physiological Responses to HIF-1α and HIF-1β.
EPO denotes erythropoietin, NOS nitric oxide synthase, and VEGF vascular endothelial growth factor.

Since these original discoveries were made, knowledge about HIFs has increased rapidly. For those of us concerned with the physiological effects of hypoxia, HIFs are of interest primarily because of their role in the regulation of a series of genes that affect the organism's response to hypoxia.

Figure 2 summarizes the great variety of effects of HIFs. HIF-1α has been shown to promote cell survival under hypoxic conditions by switching metabolism from oxidative to glycolytic. This is done by regulating the genes that increase the flux of glucose to pyruvate.[3] Although glycolysis is a relatively inefficient path for the production of ATP, as compared with oxidative metabolism, it can keep the cell alive by reducing oxygen consumption.

HIF-1α can also affect the production of ATP. It has been shown that HIF-1α–null fibroblasts (i.e., fibroblasts with both copies of the gene missing) produce higher ATP levels at 1% oxygen than do wild-type cells at 20% oxygen. But under these conditions, the HIF-1α cells die because of the buildup of reactive oxygen species. Switching to glycolysis may prevent excessive mitochondrial generation of reactive oxygen species.[4]

In addition, angiogenesis, an important response to hypoxia, is promoted by HIF-1α. For example, in patients with coronary artery disease, collateral vessels often develop in ischemic areas of the myocardium, and patients with collaterals may have smaller infarcts if the main vessel is occluded.[5] Many solid tumors outgrow their blood supply, with the result that the center of the lesion is hypoxic; HIF-1α is up-regulated in these tumors.[6] This finding has sparked an interest in the use of HIF-1 inhibitors as chemotherapeutic agents against cancer.[6]

Chronic hypoxia can cause pulmonary hypertension. This is seen in patients with chronic obstructive pulmonary disease (COPD) and in healthy people at high altitude. A low partial pressure of oxygen (P_{O_2}) causes contraction of the smooth muscle in small pulmonary arteries. Both HIF-1α and HIF-2α play a role in the response to hypoxia, in part through their regulation of endothelial nitric oxide synthase and the lower levels of nitric oxide in endothelial cells.[7]

Erythropoiesis has a close link to HIFs. Tibetans have genetic differences from Han Chinese that enable them to tolerate high altitude.[8] As a result, they have lower pulmonary-artery pressure at high

Table 1. Partial Pressure of Oxygen (Po_2) in People Residing at Very High Altitude, as Compared with Po_2 at Sea Level.*

Location	Population	Altitude	P_{IO_2}	P_{AO_2}	Approximate Pa_{O_2}
		m		*mm Hg*	
Sea level		0	150	100	95
La Rinconada, Peru	7,000	5100	77	47	43
Cerro de Pasco, Peru	75,000	4300	86	55	50
El Alto, Bolivia	1,000,000	4150	88	56	50
Lhasa, Tibet	370,000	3650	94	61	54
La Paz, Bolivia	850,000	3650	94	61	54
Leadville, Colorado	2,600	3100	100	64	58

* Shown are pulmonary values for residents of five of the highest-altitude towns in the world, as well as residents of Leadville, Colorado, the highest-altitude incorporated city in the United States. The values for the partial pressure of alveolar oxygen (P_{AO_2}) are derived from Rahn and Otis.[14] The small differences between P_{AO_2} and the partial pressure of arterial oxygen (Pa_{O_2}) are based on data from other reports. The values shown are representative; actual values differ from one person to another. P_{IO_2} denotes partial pressure of inspired oxygen.

altitude than Han Chinese[9] and a lower hematocrit.[10] HIF-2α is important in renal and hepatic erythropoietin production.

HIFs also regulate the function of the carotid body, which is responsible for the increase in ventilation that is crucial for survival at high altitude. The regulation occurs in part through mitochondrial metabolism, as noted above, and also through the production of carbon monoxide, which inhibits afferent nerve activity.[11] Other effects of HIFs include their influence on airway epithelial cells, contributing to lung development,[7] and on the permeability of vascular endothelium, contributing to lung injury.[7]

HYPOXIA AT HIGH ALTITUDE

If you mention chronic hypoxia to physicians, many immediately think of severe chronic lung disease. This is not surprising, since COPD is now the second leading cause of death in the United States, and according to one estimate, 15 million Americans currently have a diagnosis of COPD.[12] But patients with COPD have tissue hypoxia due to arterial hypoxemia, which is largely the result of a ventilation–perfusion imbalance in the lung. Environmental hypoxia, the most common cause of which is dwelling at high altitude, leads to hypoxemia as well as tissue hypoxia. This is a serious matter for the enormous number of people who live at high altitude. According to the World Health Organization, 140 million people live at 2500 m above sea level or higher.[13] Most of these people are free of disease, yet they live in a state of chronic alveolar hypoxia and often have severe hypoxemia. For example, Table 1 shows that the 1 million inhabitants of the city of El Alto, Bolivia, which is at an altitude of 4150 m, have a partial pressure of alveolar oxygen (P_{AO_2}) of approximately 56 mm Hg. Their partial pressure of arterial oxygen (Pa_{O_2}) is even lower — about half the normal value at sea level. Figure 3 shows the P_{AO_2} in permanent residents of three cities at high altitude. Thus, when we consider the prevalence of chronic tissue hypoxia, the enormous population living at high altitude should be at the top of the list.

The hypoxia of high altitude has many deleterious effects. Nearly 100 years ago, the physiologist Joseph Barcroft stated, "All dwellers at high altitude are persons of impaired physical and mental powers."[15] We can divide people at high altitude into three groups. The first group comprises visitors who go to locations at high altitude for a short period for recreational purposes such as skiing or climbing. The second group consists of sojourners, people who originally come from low-altitude locations but move to high altitudes for months or years. Many sojourners are employed in mines and other industrial activities, as well as in corporations, hospitals, schools, and embassies. The third group is the largest: permanent residents of high-altitude locations, mainly in the Andes (in South America) and on the Tibetan plateau (in Asia).

People who visit high-altitude locations are

aware of the effects of hypoxia. They notice increased shortness of breath on exertion, impaired exercise capacity, and often mild neuropsychological impairment such as difficulty in concentrating or a tendency to make arithmetic errors. Sojourners at high altitude generally report the same problems, even though they may have been at high altitude for months or years. It is often assumed that permanent residents are fully adapted to high altitude. Their work pattern is the same as that of people at low altitude, and some people have been living at high altitude for many generations.

However, it is now clear that all three groups of people — visitors, sojourners, and permanent residents — have improved maximal oxygen consumption if they descend to a lower altitude. This is usually obvious for visitors and sojourners, but careful measurements show that it is also true of permanent residents. For example, a study involving residents of Cerro de Pasco, a Peruvian city that is 4300 m above sea level, showed that their maximal oxygen consumption increased when their partial pressure of inspired oxygen (P_{IO_2}) was raised to the normal value at sea level.[16] Another study, involving Bolivians living at an altitude of 3600 m, reported the same findings.[17] These results indicate that permanent residents are not fully adapted to the altitude, since their physical capacity is improved at a value for P_{O_2} that is associated with a lower altitude.

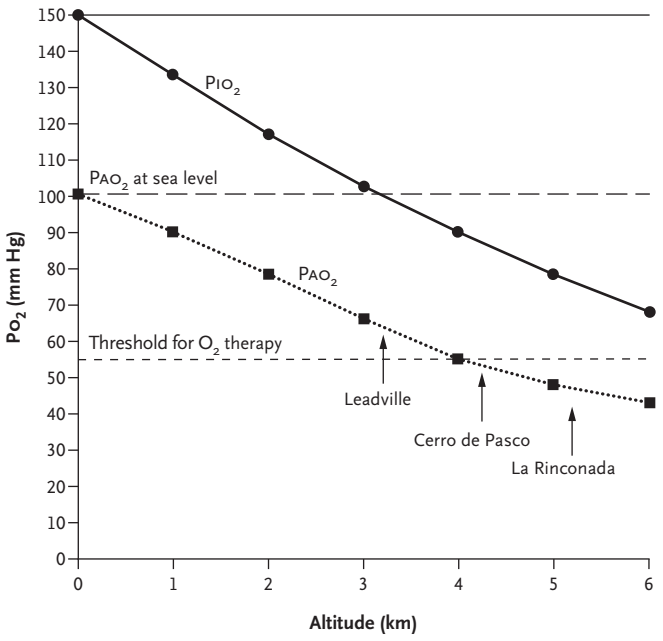

Figure 3. Partial Pressure of Oxygen in Inspired Air (P_{IO_2}) and of Alveolar Gas (P_{AO_2}) among Permanent Residents in Three High-Altitude Locations.

Data are shown for La Rinconada, the highest town in the world, and Cerro de Pasco, both in Peru, and for Leadville, Colorado, the highest incorporated city in the United States. The values for P_{AO_2} are from Rahn and Otis.[14] The values for the partial pressure of arterial oxygen (P_{aO_2}) would be lower by a few millimeters of mercury. Patients in the United States with chronic obstructive pulmonary disease who have a P_{aO_2} value below 55 mm Hg (lower dashed line) are eligible for continuous oxygen therapy under Medicare. The circles and squares represent the data points at 1-km intervals.

Neuropsychological function at high altitude is impaired in visitors and sojourners if the altitude is high enough. However, several studies have shown that groups of permanent residents at high altitude have impaired neuropsychological function, as compared with a matched group of permanent residents at a lower altitude.[18-20] Further studies are needed to confirm the findings. Studies have also shown that cognitive development in children is slowed at high altitude,[21,22] although again, additional studies are needed. The results of these investigations suggest that permanent residents of high-altitude locations may have better neuropsychological function when altitude is reduced.

The improvement in physical activity when the altitude is reduced is hardly surprising. The P_{IO_2} is increased, and presumably the P_{O_2} in the exercising muscles also rises. The same argument can be made for neuropsychological function. Presumably, the P_{O_2} in the brain is increased, along with the P_{O_2} in the rest of the body, when the P_{IO_2} is raised. This suggests that there are many people at high altitude, not only visitors and sojourners but also some permanent residents, whose physical and mental function would be improved if they moved to a lower altitude.

APPROACHES TO ALLEVIATING HIGH-ALTITUDE HYPOXIA

These findings may seem to be of only theoretical interest. Certainly, it is impracticable to expect permanent residents to relocate to a lower altitude. However, because of advances in technology, in which I have no personal financial interest, it is now possible to reduce the physiological altitude by raising the oxygen concentration in the air. This was first done about 20 years ago for single rooms, in a procedure known as oxy-

gen enrichment.[23] The process is now widely used in dormitories, mines, some luxury hotels, and ski resorts. Operation of the Atacama Large Millimeter Array (ALMA) telescope, in northern Chile, at an altitude of 5000 m, involves 400 people in oxygen-enriched rooms, and the Chinese trains to Lhasa, Tibet, which pass through regions at an altitude of 5000 m and carry more than 1000 passengers per day, are equipped with an oxygen generator in every car.[24] The oxygen is usually obtained from air with the use of a synthetic zeolite that preferentially adsorbs the nitrogen.

The extent of the reduction in physiological altitude that can be obtained by adding small amounts of oxygen is remarkable. For example, for every 1% increase in the inspired oxygen concentration, the physiological altitude is reduced by approximately 300 m.[23] Thus, in the Chinese train to Lhasa, the oxygen in the air is increased by only 3 percentage points (from 21% to 24%), but the equivalent altitude is decreased by 900 m, which is sufficient to prevent acute mountain sickness.[24] Astronomers living at an altitude of 5000 m have an inspired oxygen concentration of 28%, which reduces their physiological altitude to 3200 m, an altitude that is much more easily tolerated than 5000 m. Oxygen concentrations above 30% are not used.[25]

It is now practicable to raise the oxygen concentration in whole buildings, a process that is called oxygen conditioning to emphasize its similarity to air-conditioning.[25] Air-conditioning has a long history of improving the well-being and productivity of people in hot climates, and oxygen conditioning has the potential to do the same for some people who reside at high altitude. The costs of oxygen conditioning require further study, but the process has many similarities with air-conditioning. In both procedures, the main cost is in compressing gas. For air-conditioning, this is the refrigerant gas in the chiller, and for oxygen conditioning, it is atmospheric air from which the zeolite can preferentially adsorb the nitrogen.

One possible application of oxygen conditioning is in schools at high altitude. A recent study has shown that schoolchildren living at an altitude of 3500 m have impairment of neuropsychological function as compared with a matched group living near sea level.[26] Presumably, this means that the learning process is compromised at high altitude and that oxygen conditioning in schools at high altitude might be beneficial. Similarly, since we know that wound healing is impaired under hypoxic conditions,[27] oxygen conditioning could be valuable in hospitals at high altitude. In addition, neonatal mortality increases markedly with altitude,[28] suggesting that newborns might benefit from oxygen conditioning.[29]

Furthermore, since neuropsychological function is affected in visitors and sojourners at high altitude, and apparently also in some permanent residents, oxygen conditioning could be valuable wherever important decisions are being made. This would include facilities such as company boardrooms, banks, courtrooms, and embassies. Oxygen conditioning at high altitude is an extension of existing technology that has been shown to be beneficial, and its promise is intriguing.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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