

Acclimatization matters

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Acclimatization to hypoxia allows humans to climb to over 8000 m without supplemental oxygen (Everest is 8850 m), while exposure to the same altitude without acclimatization results in death in minutes. How does this happen? Much is known about the physiology, but discoveries are still occurring. And the whole spectrum of molecular responses driving the body to acclimatize are just beginning to be explored. The physiological phenotype of acclimatization will be reviewed, and new insights will be highlighted. Further understanding of acclimatization may lead future climbers, travelers, or hypoxic patients at sea level to mechanisms to artificially invoke acclimatization to improve safety and health.

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Current Opinion in Physiology 2019, 7:49–52

This review comes from a themed issue on **Hypoxia**

Edited by **Hesham Sadek** and **Gregg Semenza**

For a complete overview see the [Issue](#) and the [Editorial](#)

Available online 27th December 2018

<https://doi.org/10.1016/j.cophys.2018.12.006>

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Why acclimatization matters?

It is hard to overstate the profound impact on humans of acclimatization to hypoxia. Creation of a state of acclimatization transforms a situation at extreme high altitude when one only has minutes to live, compared to becoming acclimatized where there is no direct risk of death from hypoxia [1,2]. Becoming acclimatized also means that you are fortified with increased exercise capacity and improved cognitive function that is not available by any other means (Figure 1). And you are shielded from the risks of potentially fatal high-altitude illnesses such as high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE). Finally, after you descend to low altitude, acclimatization endures [3]. That means that on a future climb or exposure to hypoxia your body may react as if it was still acclimatized.

The acclimatized phenotype

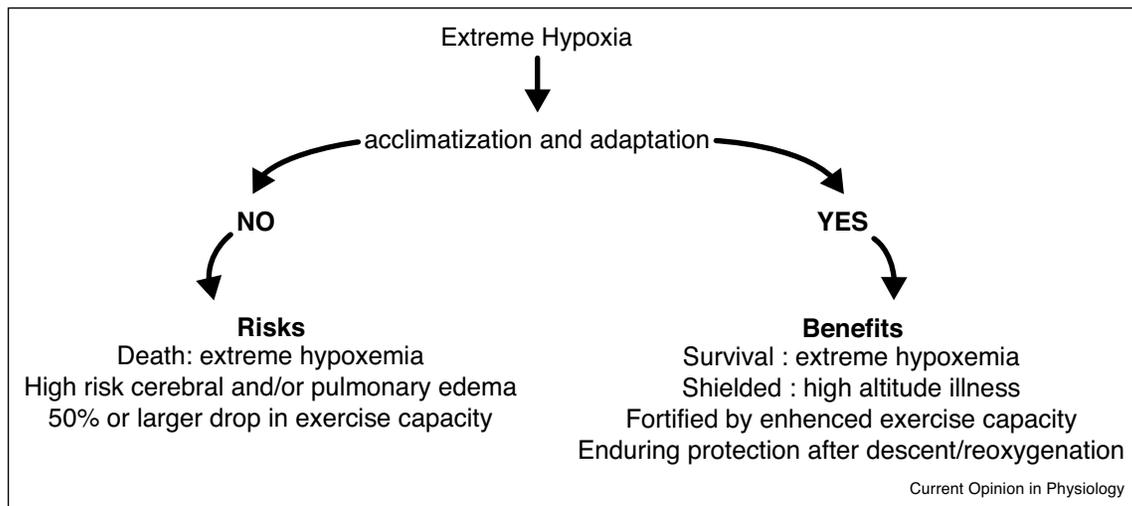
Charles Houston, writing more than 60 years ago, said ‘Acclimatization consists of a series of integrated changes

which tend to restore the oxygen pressure in the tissues toward that of the inspired air’ [1]. The severity of hypoxic stress, rate of onset, and individual physiology determine whether the body successfully acclimatizes or is overwhelmed. Importantly, acclimatization is the only known means to improve physical and cognitive performance at high altitude. No single part of the acclimatization response has been shown to be responsible; in contrast, the integration of dozens and maybe hundreds of small changes seem necessary for success. Acclimatization is driven by reducing the oxygen gradient from inspired air to the cell interior by several processes. An essential primary factor is the immediate and continued increase in ventilation, which is a highly sensitive and rapidly responding system. The increase in red cell mass acts to boost oxygen transport. Many would argue that these two responses are primary to the initiation of acclimatization. Recent discoveries suggest possible common molecular mechanisms of oxygen sensing that drive both the ventilatory and red blood cell responses to hypoxia. Additionally, skeletal muscle changes support better physical performance, and as of yet unknown mechanisms drive improvements in cognitive function.

The initial ventilatory augmentation that occurs in hypoxia, driven by carotid body sensitivity to low oxygen, is central to becoming acclimatized. The carotid bodies are sensory organs for detecting reduced arterial blood oxygen levels, and the resulting chemosensory reflex maintains cardio-respiratory homeostasis during hypoxemia [4]. However, the carotid body response to hypoxia is heterogenous across individuals [5]. In general, weak hypoxic sensing results in poor adaptation to low oxygen environments. In contrast, a robust carotid body sensitivity to hypoxia leads to rising arterial oxygen levels.

The hypoxia-inducible factor (HIF) family of transcriptional activators is critical for maintaining homeostasis under hypoxic conditions [6,7]. HIF-1 and HIF-2, which are the two best studied members of the HIF family, are heterodimers comprise an O₂-regulated HIF-1 α or HIF-2 α subunit and a constitutively expressed HIF-1 β subunit. While HIF-1 α is expressed in all cells of all metazoan species, HIF-2 α is only expressed in specific cell types of vertebrate species [7,8]. Hypoxia-inducible factors (HIFs) serve as master regulators to maintain oxygen homeostasis in every cell of the body by balancing oxygen supply and demand [7]. And specifically of importance for determining acclimatization to hypoxia, the HIF pathway plays a vital role in the carotid

Figure 1



The risks and benefits of acclimatization to hypoxia in humans. As the mechanisms that control the process of acclimatization are discovered, additional benefits may be realized.

body response to hypoxia [9]. For example, recent work by Prabhakar and Semenza [9,10**] have shown that HIF-1 α deficiency leads to selective impairment of carotid body oxygen sensing and disrupted cardio-respiratory homeostasis. The HIF pathway is also key to the rise in blood erythropoietin levels and the resulting increasing red blood cell concentrations that accompany acclimatization. For these reasons, we consider that HIF is central to the regulation of acclimatization to hypoxia in humans.

Acclimatization and exercise

Maximal and submaximal human exercise performance during acclimatization has been extensively studied at high altitude. Maximal exercise performance seems not to change much after the initial large fall with ascent from low altitude [11–21]. For example, going from 490 m to 5533 m results in a 53% drop in VO₂Max [22], in line with other reports [23]. Contrasting the lack of improvement in maximal exercise performance measured by VO₂Max or similar parameters is the mountaineer's perception of less effort given to do the same work as acclimatization progresses at the same altitude. This paradox has led investigators to carefully examine submaximal work performance in hypoxia [3,17,22,24,25]. Early studies showing markedly improving submaximal endurance performance of up to 45% after acclimatization [25] set the stage for a recent work exploring potentially explanatory mechanisms. Two recent studies at very high altitudes showed after acclimatization in 53 subjects no improvement in VO₂Max at 5200–5500 m [3,22]. In contrast, improvements were observed in a field test of submaximal running/

climbing performance in both studies [3,22] and improved net efficiency at submaximal workloads was reported by Latshang *et al.* [22].

Additionally, Subudhi *et al.* took their subjects to low altitude for 7 days after acclimatizing to 5200 m for 16 days. They then re-ascended to 5200 m and repeated the field running test. Subjects ran just as well at 5200 m after a week of low altitude living as they did after 16 days of living at 5200 m [3]. A serendipitous finding was that subject's hemoglobin levels fell significantly during that week at low altitude, perhaps due to the selective destruction of the youngest circulating red cells (neocytolysis) [26,27]. The result was that arterial oxygen content was on re-ascent the same as it had been on acute exposure, suggesting that during acclimatization, the rising hemoglobin concentration and thus arterial oxygen content is not critical to improving submaximal endurance capacity. This finding awaits further experimental validation and exploration. Latshang *et al.* speculate additional mechanisms of improved submaximal exercise performance after acclimatization to include changes in basal metabolic rate, a decrease in sympathetic activation (unlikely in light of evidence from Hansen *et al.* at similar altitudes [28]), nutritional changes, decreased myocardial oxygen consumption, or a reduction in body weight [22].

Skeletal muscle metabolism to support improved exercise performance in hypoxia

Prior reviews and studies describe the changes that occur in skeletal muscle to support muscular work in hypoxia

[29–31,32^{••},33,34^{••},35]. Recently, we studied a group of lowland residents at sea level and after they acclimatized to high altitude (5200 m). Chicco *et al.* showed that combining *ex vivo* examination of oxidative phosphorylation, and metabolomics and proteomics on frozen muscle biopsy samples, showed a unique pattern of acclimatization to hypoxia. In contrast to the view that hypoxia downregulates aerobic metabolism [35], results show that in healthy humans acclimatizing to high altitude hypoxia, the mitochondria play a central role in muscle hypoxia adaptation. They achieve this through a rise in the resting phosphorylation potential and enhancing the efficiency of oxidation of long-chain acylcarnitine. This directs higher amounts of muscle glucose toward pentose phosphate and one-carbon metabolism pathways that, in turn, support cytosolic redox balance. The accumulation of free amino acids supports these changes by integrating cytosolic and mitochondrial pathways serving to remove excess nitrogen from the cell. Thus, anaerobic metabolism and aerobic metabolism are tightly linked in hypoxic skeletal muscle at rest, with an unexpected role for protein catabolism and allosteric regulation to control skeletal muscle metabolism at rest in hypoxia. Future studies of the time course of these changes, ranging from normoxia at sea level to hours then days and weeks in hypoxia, may reveal the signaling pathways controlling these responses in skeletal muscle.

Acclimatization endures

Attempts to conquer the world's highest peaks (>8000 m) support the notion that gradual acclimatization to low O₂ tensions bestows a unique resistance to hypoxia so that the individual lives and performs at altitudes which would result in unconsciousness and death if the ascent were to occur rapidly. The first evidence of the persistence of acclimatization to hypoxia came from Luft and his experiments on climbers before and after the German Himalayan expedition to Nanga Parbat in 1938 [36]. Before embarking on the expedition, these members were tested in the decompression chamber to provide control observations. Most of the participants were observed for 6–8 weeks after returning to sea level. The erythrocyte count and hemoglobin concentration of these climbers decreased rapidly on the return to sea level. In an altitude challenge, incremental increases of 1000 m per five minutes were used. The ascents were conducted until the handwriting results showed severe alterations. In 7 of 8 climbers, an increase in altitude tolerance of 1000 m was apparent even 8 weeks after leaving the mountain. The improved tolerance persisted for 6 months. Luft attributed the persistent cognitive ability post-expedition to the subjects ventilating more post-expedition, resulting in higher alveolar PO₂ levels.

More recent studies support persistence of acclimatization after descent to low altitude [3,11,37–39]. For example, Beidleman *et al.* recently showed acclimatization-induced improvements in ventilatory and hematologic

responses, acute mountain sickness, and cognitive function that were partially retained during re-ascent after 12 days at sea level [39]. And Subudhi *et al.* showed similar findings after low altitude residence for 7 and 21 days following 16 days acclimatization to 5200 m [3]. However, the mechanisms driving these persistent responses remain unknown.

Conclusion

The human body can adjust to low oxygen levels resulting in a profound protection from the detrimental effects of hypoxia. The recent discovery of the HIF pathway will lead to the mechanisms controlling acclimatization that are (a) dependent on HIF and (b) alternate, non-HIF dependent pathways that determine the success of human acclimatization to hypoxia. We are left to imagine discovering the mechanisms of acclimatization responsible for inoculating the human body against the ravages of hypoxia. Apparent beneficiaries are mountaineers and tourists, and workers living at or traveling to work at, high altitudes. But also consider the patient on supplemental oxygen secondary to heart or lung disease. If the mechanisms underlying adaptation to hypoxia in normal, healthy people could be artificially induced in those patients would that improve their health and well-being?

Conflict of interest statement

Nothing declared.

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Papers of particular interest, published within the period of review, have been highlighted as:

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