

Adaptation and maladaptation to high altitude hypoxia – from noble prize to noble gas

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With ascent to high altitude barometric pressure declines, leading to a reduction in the partial pressure of oxygen (PO_2) at every point along the oxygen transport chain from the ambient air to tissue mitochondria. This leads, in turn, to a series of changes over varying timeframes across multiple organ systems that serve to maintain tissue oxygen delivery at levels sufficient to prevent acute altitude illness and preserve cognitive and locomotor function. While the pattern of these responses, collectively referred to as acclimatization, are similar across individuals, the magnitude of such responses demonstrates significant interindividual variability, which accounts for subsequent differences in tolerance of the low oxygen conditions in this environment.

At the cellular level, a central factor for high altitude acclimatization - for whose characterization the Nobel Prize in Medicine was awarded in 2019 - is hypoxia-inducible factor (HIF)-1. HIF-1 is a gene transcription factor that serves as the master regulator of cellular responses to hypoxia, including but not limited to cellular metabolism, angiogenesis, and erythropoiesis. If the adaptive processes fail to compensate sufficiently for the decrease in oxygen availability, acute mountain (AMS), high altitude cerebral edema (HACE), or high altitude pulmonary edema (HAPE) may occur. These diseases may develop in non-acclimatized individuals after ascending too fast to altitudes above ~2.500 m. While AMS is an unpleasant but generally harmless condition that is self-limited, HACE and HAPE are life-threatening emergencies, which can be fatal if not treated promptly. For the prevention and treatment of AMS and HACE the carbonic anhydrase inhibitor acetazolamide and the corticosteroid dexamethasone are the drugs of choice, while for the prevention and treatment of HAPE pulmonary vasodilators such as nifedipine or phosphodiesterase-5-inhibitors (sildenafil, tadalafil) are recommended.

In the search for methods to shorten the duration of acclimatization prior to high altitude expeditions, one novel approach was implemented during a Mount Everest (8.849 m) expedition in spring 2025 – inhalation of the noble gas xenon. Despite the tremendous attention this approach received in the media, evidence of benefit is lacking and there is reason to believe other aspects of the expedition protocol contributed significantly to the summit success. Thus, xenon inhalation as pre-acclimatization method cannot be recommended.