TITLE

Accompanying video: https://youtu.be/-aLUnCLkuYU?t=2364

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CONTENT

Physiological responses to hypoxia: Today we known that there is a reduction of barometric pressure with increasing altitude and, as a consequence, partial pressure of O2 in the inspired air is reduced. This means that in the O2 cascade from air to mitochondria there is a reduction of the pressure gradient over which the diffusion of oxygen can take place and the ability of peripheral tissues of producing energy or ATP becomes impaired. To cope with these changes several physiological modifications take place immediately after exposure to hypoxia as well as during prolonged permanence at altitude. Thus, a rapid ascent to high altitude is likely to result in death whereas a slow ascent can be successful when accompanied by adaptations which compensate for the lack of oxygen reaching the tissues and guarantee a continuous production of ATP in the peripheral tissues. The compensatory mechanisms activated in response to hypobaric hypoxia involve respiratory, cardiovascular and peripheral tissues. The physiological responses to hypobaric hypoxia are diverse and numerous, changing across hours, days, and weeks. Moreover, their magnitude exhibits significant inter-individual variation to which genetic variation likely contributes substantially. One of the most known effect of going at altitude is the reduction of exercise capacity, classically represented by a reduction of maximal oxygen consumption. Usually, VO2max data obtained in subjects acutely exposed to altitude are slightly lower than those obtained in subjects with similar characteristics after several days of exposure to hypobaric hypoxia. This difference is due to physiological adaptations occurring across days at altitude such as increase in pulmonary function, changes in the cardiovascular system and blood O2 carrying capacity.

Molecular basis of adaptations to hypoxia: Many of the physiological changes reported before are associated with the activation of a specific molecular pathway that involves the stabilisation of the hypoxia-inducible factor (HIF) family of transcription factors. Hypoxia-inducible factors (HIFs) are central regulators of cellular responses to hypoxia and cellular metabolism. HIF-1 is a heterodimer composed of two subunits. Both subunits are actively expressed in normoxic conditions but HIF-1α is rapidly degraded because of hydroxylases (PHDs) that leads to its ubiquitinylation by von Hippel Lindau protein and subsequent proteasome-mediated degradation. In hypoxia, PHD activity is inhibited thereby preventing HIF-1α degradation and increasing its levels. HIF-1 nuclear translocation and binding to hypoxia response elements (HREs) within gene promoters drives transcriptional activation of genes involved in tissue perfusion, cell survival and glycolytic metabolism that are needed for tissue protection in hypoxic conditions and regulation of inflammation.

Role of nitric oxide in the adaptations to hypoxia: NO is a gaseous signaling molecule with several physiological functions in the human body. Endogenous NO production occurs via two distinct and uniquely different pathways: i) NO can be produced via oxidation of the semi-essential amino acid L-arginine by a reaction catalyzed by the NO synthase (NOS) enzymes. This reaction requires O2 as a co-substrate. As soon as it is produced, NO can exert its function locally or rapidly oxidate to nitrite and then nitrate. ii) the alternative pathway for NO generation involves the NO3-NO2 reduction to NO. Notably, The NO3-–NO2-–NO pathway is O2 independent, been considerably enhanced in hypoxic conditions. It is therefore viewed as an important ‘‘back-up’’ system for maintaining and/or enhancing NO

bioavailability and signaling in hypoxic environment. Several studies have demonstrated that nitrate can be increased by the ingestion of food rich in this compound. Augmenting the NO3−- NO2−-NO pathway by diet may therefore have potential as an ergogenic aid in hypoxic conditions such as acute hypoxia and at high altitude. As previously reported, HIF-α protein is normally produced and rapidly degraded in the presence of oxygen whereas with hypoxia, HIF-α protein accumulates and translocates to the nucleus where it binds to the HIF-β subunit to activate target genes. It is interesting to note that, even with enough O2 for HIF-α hydroxylation, the presence of NO can result in HIF-α protein stabilization by direct interaction of NO with HIF-α since it compete with O2 or S-nitrosylation of pVHL. These reactions allow HIF-α to escape the degradation pathway so that the accumulated HIF-α in the cytosol translocates to the nucleus and binds and dimerizes with HIF-1β, activating transcription of HIF-dependent genes.

Experimental evidences of the importance of NO in hypoxia: The first examples come from animal world. Among vertebrates there are some who are able to tolerate long periods of oxygen deprivation. The painted and red-eared slider turtles and the crucian carp are the most extreme and can survive even months of total lack of oxygen during winter. It has been demonstrated that the key to hypoxia survival resides in concerted physiological responses, including strong metabolic depression, protection against oxidative damage and–in air-breathing animals–redistribution of blood flow. Each of these responses is known to be tightly regulated by nitric oxide (NO) and during hypoxia by its metabolite nitrite. Indeed, these animals show the highest nitrite reductase activity in the animal world. Among humans, the most important come from populations physiological adapted to survive at high altitude from generations. These populations, like Tibetans, show specific physiological responses to hypoxia that are highly related to elevated nitric oxide bioavailability. A role for NO in hypoxic adaptation was first recognized after it was observed that concentrations of exhaled NO are substantially higher among two high-altitude-dwelling populations under chronic hypoxic stress. Moreover, Tibetan highlanders living at 4,200 m and Bolivian Aymara living at 3,900 m have a superior ability to tolerate hypoxia – as judged by better physical performance at altitude – than does the general populace, and they also show elevated NO bioavailability. Although it was supposed that primary effect of NO was at pulmonary level, today we know that NO has a likely wider role beyond the lungs. The effects of this additional NO load on the dynamics of the peripheral circulation are marked, as indicated by forearm plethysmography measurements which showed that Tibetan highlanders had double the forearm blood flow when compared to a sample of sea-level residents. In lowlanders, it has been demonstrated that altitude exposure induces changes in nitrate and nitrite plasma concentrations. Moreover, some possible consequences of high altitude exposure (HAPE, pulmonary vasoconstriction, hypoxic exercise vasodilation) are mediated or can be prevented by elevated NO bioavailability. Thus, NO seems to play an important role in physiological adaptations to hypobaric hypoxia both at central and peripheral level. Although there are clear evidences about the importance of NO in regulating some physiological mechanisms induced by hypoxia exposure, evidences from studies increasing NO bioavailability by NO3- supplementation are contrasting. Up to date it seems that enhancing NO may potentially be beneficial for the wide variety of individuals ascending to altitude each year. However, further studies addressing these issues are needed.

Questions

What are the classical physiological adaptations in response to hypobaric hypoxia?

Are there any differences between acute and chronic hypoxia from a physiological prospective?

What is the role of nitric oxide in the physiological adaptations to hypoxia?

How can nitric oxide interact whit hypoxia-inducible factors?

How can high-altitude populations cope with chronic reduction of pO2? Is this related to nitric oxide?