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Cell. Mol. Life Sci. (2009) 66:3537–3538
DOI 10.1007/s00018-009-0140-1
Cellular and Molecular Life Sciences

MULTI-AUTHOR REVIEW

The impact of hypoxia on our body: from integrative physiology to human disease

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Received: 18 August 2009 / Accepted: 20 August 2009 / Published online: 3 September 2009
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There would be no higher forms of human life on earth without oxygen. Throughout existence our bodies have relied on a constant and continuous supply of oxygen. In circumstances where oxygen availability is reduced (hypoxia), the inherent physiologic responses that are initiated through both cellular as well as systemic mechanisms are beginning to be understood. The very early and fascinating studies that were performed over a century ago had "volunteers" (read: adventurers) exposing themselves by climbing high mountains just to attain hypoxic environmental conditions. At the beginning of the twentieth century the only concern regarding hypoxia was related to situations involving pulmonary disease, anemia and ascent to high altitude. In the last 2 decades, however, the ever increasing reach of hypoxia has become much more evident. Hypoxia plays a crucial role in almost all acute and chronic diseases including, but not limited to, kidney and liver diseases, pulmonary hypertension, most forms of cardiovascular disease including atherosclerosis, stroke, ischemic diseases, retinal degeneration, wound healing, several pathologies of the CNS, inflammation, transplantation, acute or chronic mountain sickness and—last but not least—tumorigenesis. In addition to these pathological conditions, reduced oxygenation occurs also under normal physiologic circumstances, namely during embryonic development, physical activity and ascent to high altitude. On one hand the impact of hypoxia has attracted many basic scientists into the field of oxygen sensing and oxygen-dependent gene expression. This explosion of enthusiasm has been very fruitful, and several mechanisms of the molecular response to hypoxia have been unraveled. On the other hand, many physiologists and clinical researchers have focused on hypoxic adaptation and acclimatization in exercising humans, including elite athletes and extreme mountaineers. The time has come for the basic researchers working in the field of molecular hypoxia to come together with their colleagues who have been examining the hypoxic response in human volunteers and patients. The last few international "hypoxia" meetings have successfully initiated the integration of these two groups. One of those meetings—which I had the honor to organize—was held for the second time at Monte Verità in Ascona, the Italian-speaking region of Switzerland, at the end of 2007. At the "Mountain of Truth," approximately 70 world-leading investigators in the molecular, physiologic and clinical fields of hypoxia met to discuss topics ranging from translational aspects of integrative biology to human disease. By this time, I was kindly asked by the editors of CMLS to select a few "hypoxic" topics that could be of interest for their widespread readership. I am glad that most of the colleagues that I invited to share their work enthusiastically agreed to contribute. The realization of this multi-author review might have taken longer than expected, but the present reviews are excellent, reader-friendly and up to date.

Nature considers sufficient oxygen supply to each single cell so important that all cells in our body are able to sense oxygenation and respond to hypoxia within seconds to minutes. Remarkably, every single cell constantly synthesizes factors that are primarily stabilized only in the

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presence of hypoxia. Prominent among these factors are the hypoxia-inducible factors (HIFs) that under normoxic conditions are basically degraded immediately after being synthesized. This is an energetic burden for the cell but allows for an instantaneous response when oxygen supply is reduced. Pugh and colleagues brilliantly summarize—with their well-known British humor—the fascinating molecular interplay between oxygen, HIFs and prolyl hydroxylases (PHDs). Building upon this fundamental knowledge, Antoniou and Ogunshola move from molecules directly to Alzheimer's patients, questioning whether hypoxically induced HIF-1 stabilization mediates neurodegeneration. What is the connection between low oxygenation and this disease? The brain's extreme sensitivity to hypoxia may lead to severe alterations of the brain's function by rapidly disturbing neuronal homeostasis. Apart from Alzheimer's, hypoxia has been implicated in many more neurological diseases such as Parkinson's disease and stroke.

Every reader knows that trekking in the beautiful Altiplano at 3–4,000 m above sea level will make everyone breathless in one way or another. Adequate oxygenation of every single cell requires efficient oxygen uptake from the air by the lungs. Even under physiological conditions, the environmental oxygen supply might change and thus ventilation must adapt accordingly. Joseph and Pequinot explain in their review how ventilation acclimatizes in response to such a hypoxic challenge. This acclimatization requires a complex reorganization in both the peripheral (carotid bodies) and the central (brainstem respiratory groups) chemoreceptors. Once ventilation is elevated, the oxygen uptake by the erythrocytes increases too. Soliz and myself asked the question as to whether there is a HIF-target gene that might regulate both the respiratory and the hematopoietic response to hypoxia. Indeed, we show that the "old blood hormone" erythropoietin (Epo) plays a crucial role in ventilation by interacting with carotid bodies (systemic Epo) as well as with the respiratory groups (cerebrally produced Epo). Of note, during the last decade it has become evident that Epo has far more functions apart from enhancing red blood cell production, with most of these functions associated with neuroprotection. As such, Monge and colleagues present new insights in Epo's protective role on auditory hair cells of the inner ear: Epo reduced the gentamicin-induced hair cell damage.

Despite all the protective mechanisms we possess, acclimatization to reduced oxygenation, such as that which is experienced at high altitude, might fail. Typically, this so-called acute mountain sickness (AMS) is observed in mountaineers who ascend to high altitudes too rapidly. Obviously, nature did not consider the use of cars, gondolas, air transport or the top-end equipment that allow fast ascent to the roofs of this world. AMS and the resulting high altitude cerebral edema (HACE) are life-threatening, as we will see in the very comprehensive review by Bailey and colleagues. By applying diffusion-weighted magnetic resonance imaging (MRI), they provide new insights into the development of HACE.

What about your heart at altitude, especially if you plan extensive physical activity? Highlanders are used to exercise at high altitude and show, accordingly, advantages over lowlanders who want to compete with them. Remember the disputes concerning soccer games in La Paz! Moreover, some athletes seek altitude training to improve their competition performance. Calbet—definitely a lowlander living on an island—and his colleagues describe in their review the impact of acute and chronic hypoxia on the heart's function. This topic is followed by an overview focusing on the exercising skeletal muscle at hypoxia. Lundby and his athletic colleagues review the fact that the working muscle becomes hypoxic already at sea level and that oxygenation of the skeletal muscle is further challenged by exercising at high altitude.

Hypoxia is everywhere. We constantly face physiological or pathological hypoxic conditions whether it is systemically, locally or at the cellular and molecular levels. I am convinced that within the next few years the knowledge of hypoxic signaling pathways will enter common clinical application. Most probably, hypoxic preconditioning of cells, organs (organ transplantation) and perhaps even patients will be fashionable.

As you realize, the presented topics are fascinating and more is to come! I deeply apologize for not having asked all our participants for their interesting contributions, but I do hope to have balanced the reviews as envisioned: from molecules to men. Thank you all for your dedication to "hypoxic science."