HIGHLIGHTED TOPIC | Hypoxia

Translation in progress: Hypoxia

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RECENT DISCOVERIES OF MOLECULAR oxygen sensors in the hypoxia-inducible factor (HIF) system (1, 9–11) have brought together systems physiology and genomics in an exciting, wide-ranging exploration of how humans and other organisms sense and respond to hypoxia. Reflecting this growing and widespread interest in hypoxia, PubMed “hypoxia” citations have doubled in the last decade, to over 50,000 published articles. Since 2000, this is the third Highlighted Topic in the Journal of Applied Physiology with an emphasis on hypoxia (13, 14), indicative of the rapid, continuing evolution of the topic. The reviews that appear in this current Highlighted Topic originated from the 18th International Hypoxia Symposium that took place in Lake Louise, Canada in February 2013. The biannual International Hypoxia Symposia (IHS) bring together scientists and clinicians to focus on the integrative and translational biology of hypoxia, and because of the profound and protean biological impacts of hypoxia, the topics covered are diverse. The unique emphasis on integration of basic science with clinical medicine that distinguishes the IHS is reflected in the following six mini-reviews from leaders in this vigorous field. Taken together, they provide an overview of current stimulating topics in the biology of hypoxia and offer enticing clues for future research.

The first review by Chapman et al. (2) addresses a key question for sports physiologists, trainers, and athletes: if one trains at high altitude to improve low-altitude athletic performance, when is the ideal time to compete after return to low altitude? Altitude training is now nearly universal for competitive “aerobic” athletes, but the data to answer this fundamental question are limited. The Journal of Applied Physiology has a long history of interest in this general topic (4, 7), and this newest review objectively explores the physiological parameters involved in picking the optimal time for peak performance on return from high-altitude training. The authors conclude that the time-dependent processes of neocytolysis, ventilatory de-acclimatization, and altered biomechanical factors with return to low altitude all need to be considered in relation to the exact athletic event. This fresh look at the question will help establish a better scientific basis for recommendations and also encourage more research on this important and practical issue.

In the second review, Immink et al. (5) examine the role of balance between PaCO2 and PaO2 in syncope, with implications for the overall control of the cerebrovascular circulation. They point out that despite a transient drop in cerebral blood flow with hypocapnia, it is insufficient to cause loss of consciousness, even with postural stress. However, when combined with decreased cardiac output, syncope may result. Whether hypoxemia, cardiovascular disease, or problems with cerebral blood flow/control may increase the likelihood of syncope with hyperventilation is an unanswered important issue. Joyner and Casey (6) present an intriguing synthesis of their work on the tight coupling of oxygen demand and supply during exercise and the redundancy of mechanisms serving to maintain oxygen delivery in hypoxia or hypoperfusion. This review is highlighted because of its implications for clinical medicine as well as elegant physiology. Dempsey et al. (3) in the fourth piece in the series review the mechanisms of cardiorespiratory acclimatization and deacclimatization to hypoxia and then discuss the pros and cons of such adjustments in terms of arterial oxygenation, the work of breathing, sympathoexcitation, systemic blood pressure, and exercise performance. They provocatively caution that the same deleterious cardiovascular impacts of intermittent hypoxia, such as those seen in patients with sleep apnea, may also apply to athletes upon return to low altitude from high-altitude training. This could also apply to persons with more transient intermittent altitude exposure, and their speculation will hopefully lead to appropriate investigation. The final two reviews in the series focus on two important roles of HIF. Shimoda and Laurie (12) discuss the importance of the HIF system in pulmonary vascular responses to hypoxia and the potential for pharmacologic modification of those responses. Targeting downstream HIF products offers an opportunity for treating pulmonary hypertension and also other HIF-related maladies. In the final paper in the series, Petousi and Robbins (8) review the exciting recent genomic work showing natural selection acting on oxygen-sensitive genes in Tibetans. Importantly, they point out that integrative systems physiology must be combined with genomics to further our understanding of human evolution in response to high-altitude hypoxia.

These reviews by Shimoda and Laurie and Petousi and Robbins we think highlight an important need and an opportunity for readers of the Journal of Applied Physiology in the area of hypoxia research.

Many of us are confronted daily with new findings from genomics or another arm of the omics revolution, absent any integration or translation to systems physiology. But rarely do we see a careful integration of genomics and physiology as suggested above for the role of hypoxia in pulmonary hypertension or in the global physiological responses to hypoxia of high-altitude natives. This approach can be extended to almost any area of hypoxia research, from altitude training, the control of the pulmonary or cerebral or skeletal muscle circulation, to how high-altitude natives outperform all others at high altitude.
In summary, major future advances in hypoxia research will come from physiologists and clinicians working together with genomic scientists to understand the integrated systems physiology of human responses to hypoxia. This paradigm will continue to be the purpose of the International Hypoxia Symposia and of Highlighted Topics such as this.

DISCLOSURES
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REFERENCES