HIGHLIGHTED TOPIC | Hypoxia 2015

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HOW HUMANS AND OTHER ORGANISMS sense and respond to hypoxia is a rapidly growing research field, with more than 19,000 MedLine citations on hypoxia in the last 2 years alone. Reflecting the growing and widespread interest in hypoxia, this is the fourth Highlighted Topic in the Journal of Applied Physiology with an emphasis on hypoxia(13, 16, 17). The reviews that appear in this current Highlighted Topic originated, in part, from the 19th International Hypoxia Symposium that took place in Lake Louise, Canada, in March 2015. The biannual International Hypoxia Symposia (IHS) are dedicated to bringing together the best basic scientific and clinical minds to focus on the integrative and translational biology of hypoxia. The product from 2015 is represented here in the 20 minireviews and in the dozens of long-lasting, productive scientific collaborations that have been fostered in this congenial, cross-disciplinary environment. In addition to the minireviews from the IHS, there are 14 other papers that were submitted for the Highlighted Topic in Hypoxia. The reader will enjoy the diverse topics that reflect the broad biological impacts of hypoxia.

The minireviews start in the November issue with a fascinating description of the genetics of the Denisovans (7), an archaic population of unknown origin recently discovered in Siberia. The Denisovans contributed a genetic mutation conferring favorable response to high-altitude hypoxia to modern-day Tibetans. This is followed by two reviews of remote ischemic preconditioning, the phenomenon wherein an ischemic stress can be applied to a limb, for example, and meaningful protection from future ischemic or hypoxic injury can occur in a remote organ, such as the heart or brain (11). This technique is also proposed for prevention of acute mountain sickness (1). They give the reader a concise overview of the field and summarize future directions.

Rounding out the November issue are four minireviews from leading experts on hypoxia signaling. We first learn of the intricate and robust connection of hypoxia inducible factor (HIF) signaling in the carotid body signaling and the adrenergic control of blood pressure in the rat during simulated sleep apnea (14). Translation of these findings to humans will be an exciting adventure in modern integrative physiology. Next is new work on the role of hypoxia signaling pathways in dampening lung inflammation and thus facilitating lung protection during acute lung injury (21). For hypoxic pulmonary hypertension, new ideas about blocking vascular remodeling are reviewed with a focus on hypoxia-driven metabolic and inflammatory changes in pulmonary macrophages and fibroblasts (18). This section finishes with a review of the yin and yang of adenosine in animal and human responses to hypoxia (10). In acute hypoxia, adenosine improves oxygen availability beyond the previously described effects on skeletal muscle vasodilation. In contrast, in chronic hypoxia, prolonged and excessive extracellular adenosine may have detrimental effects. Managing these different adenosine responses may lead to better adjustments in both acute and chronic hypoxia.

The December issue starts with two reviews of iron balance in hypoxia. The link between hypoxia inducible factor signaling and iron availability in hypoxic pulmonary hypertension is expertly reviewed. Understanding the sensitivity of the HIF-hydroxylase enzymes to both oxygen and iron leads to understanding of a complex system open to much further investigation for human health in both high altitude illnesses and chronic cardiopulmonary disease (4). This topic is then expanded with particular focus on the role of hepcidin in controlling iron balance in hypoxia (5). Together these two reviews underscore the importance of adequate iron stores for human adaptation to hypoxia.

Next are three reviews on different aspects of the complex physiological responses to intermittent hypoxia. The first highlights the CNS mechanisms whereby nocturnal intermittent hypoxia results in increased sympathetic nerve discharge and hypertension that persist (12). Building on these ideas is a review that focuses on the central roles of endothelin-1 and angiotensin II in mediating the sympathetic and hemodynamic response to intermittent hypoxia in animal models of obstructive sleep apnea (22). In the third review on intermittent hypoxia we learn of a novel application of repeat intermittent hypoxia exposure as an adjunct for neurorehabilitation in spinal cord injury (6).

The intricate physiological responses to sleep at high altitude are artfully reviewed in Ref. 2. Despite the many studies of sleep in hypoxia, this review points out that we still have much to learn. This includes the effect of age and sex on hypoxic sleep, the sleep physiology of highlanders, and whether these investigations can tell us more about patients with chronic hypoxia due to cardiorespiratory disease. In the final paper in the November issue, we learn about humans with excessive erythrocytosis through the creative matching of genomics to physiology, furthering our understanding of normal physiology and pathophysiology (20).

In the January issue, seven Highlighted Topic minireviews focus on medical and physiological aspects of people experiencing hypoxia. The first review (19) offers a fascinating look at how two drugs often used to prevent and treat high-altitude illnesses, acetazolamide and dexamethasone, may act by mechanisms only recently discovered, and then examines what new lessons can be learned about high-altitude pathophysiology
from these ideas. The mechanisms by which hypoxia controls skeletal muscle vasodilation are complex and redundant, and many new insights are offered in Ref. 3. The largely unexplored field of systemic hypoxia measured at the level of the microcirculation and mitochondria during shock is the focus of the next review (8). The importance of a mismatch whereby resuscitation relieves systemic hypoxia, but the microcirculation still suffers from lack of blood flow leading to tissue hypoxia challenges many precepts of shock physiology. In an engaging historical review, the birth of pulse oximetry is put into the context of early high-altitude studies (15). In the last two articles, the focus returns to the hypoxic brain in high-altitude illness, with one review exploring new understanding of the understudied cerebral venous circulation (23), and the other focusing on the limitations of current knowledge of cerebral spinal fluid physiology and its impact on future investigations of the role of intracranial pressure in high-altitude illness (9).

In summary, we believe this series of minireviews constitutes a roadmap for future investigative endeavors in hypoxia research. And furthermore, we propose that 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. Supporting collaboration to address this paradigm will continue to be the purpose of the International Hypoxia Symposia and of Highlighted Topics such as this.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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