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1 **Translation in Progress: Hypoxia 2017**

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12 How humans and other organisms sense and respond to hypoxia is a rapidly growing research
13 field, with more than 18,000 MedLine citations on hypoxia since the last JAPPL Highlighted
14 Topic in this area in 2015, and more than 80,000 since this series first appeared. Reflecting the
15 growing and widespread interest in hypoxia, this is the fifth Highlighted Topic with emphasis on
16 hypoxia in the *Journal of Applied Physiology* (23, 24, 27, 28). The invited mini-reviews in this
17 current Highlighted Topic originated from the 20th International Hypoxia Symposium that took
18 place in Lake Louise, Canada, in February 2017. The biannual International Hypoxia Symposia
19 are dedicated to bringing together the best basic scientific and clinical minds to focus on the
20 integrative and translational biology of hypoxia (See: www.hypoxia.net). In addition to dozens
21 of productive scientific collaborations fostered in this congenial, cross-disciplinary environment,
22 keynote speakers have produced 18 mini-reviews that appear in successive issues this fall. The
23 Journal has also accepted other research papers (2, 3, 6, 9, 12, 13, 16, 20-22, 25, 29) and related
24 mini reviews (10, 14) for this Highlighted Topic in Hypoxia. Readers will enjoy the diverse
25 topics reflecting the broad impact and translation of hypoxia on many areas of physiology and
26 medicine.

27

28 **OCTOBER**

29 The Hypoxia Symposium mini-reviews start in the October issue with a fascinating paper by
30 Fago (10) on globins – hemoglobin, myoglobin, and the more recently discovered neuroglobin
31 and cytoglobin – as the heme-containing proteins ubiquitously expressed in vertebrates. These
32 globins serve a broad range of biological functions, directly or indirectly related to the tight
33 control of oxygen and its toxic products in vivo. Understanding these globin proteins in hypoxia-

tolerant ectotherms will help clarify the adaptive mechanisms for surviving extreme fluctuations of oxygen availability that are detrimental to mammals. Two unique 'champions' of surviving extremes of O₂ tension are outlined in two further reviews. First, Brauner and Harter review the unique O₂ transport system of teleosts (5). These teleosts comprise 95% of fish species, and almost half of all vertebrate species, representing one of the most successful adaptive radiation events among vertebrates. In salmonids, studies indicate that hemoglobin-oxygen (Hb-O₂) unloading to tissues may increase 2-to-3 fold under some conditions without changes in perfusion. This is accomplished through the short-circuiting of red blood cell (RBC) pH regulation resulting in a large arterial-venous pH difference within the RBC and induced reduction in Hb-O₂ affinity. Next, Lague reviews the physiology of birds that live and migrate at altitude (18). Bar-headed geese (*Anser indicus*) fly across the Himalaya and Tibetan plateau during their migration. Although the majority of birds exhibit enhancements at each step of their O₂ transport cascade that help to support the high flux of O₂ required for flight and endothermy, these adaptations are further enhanced at each level of this transport cascade in the bar-headed goose. It seems that rearing at high altitude (i.e. phenotypic plasticity) also facilitates these impressive adaptations.

Related to erythrocyte regulation, Sun et al. (32) provide an up-to-date review of work on erythrocyte purinergic signaling. Collectively, these studies have reported that adenosine signaling, coupled with 5' AMP-activated protein kinase and the production of erythrocyte-enriched bioactive signaling lipid sphingosine 1-phosphate, regulate erythrocyte glucose metabolism for improved O₂ delivery. Moreover, an adenosine-dependent "erythrocyte hypoxic memory" was discovered which might provide an explanation for fast acclimation upon re-ascent

to high altitude. Interestingly, the mechanisms involved in regulation of blood volume, particularly total red blood cell volume, remain poorly understood in humans. The current state of knowledge, including the understanding of the kinetics, the putative mechanisms and the physiological relevance of the altitude-induced reduction in plasma volume and expansion in RBC volume is concisely reviewed by Siebenmann et al (26). Closely intertwined with RBC homeostasis and hypoxia is iron status. Expanding on our knowledge of the tight integration of iron homeostasis and oxygen sensing is the artful review by Lakhal-Littleton and Robbins (19) offering insights into iron and the heart. These insights include the recognition that the hepcidin/ferroportin axis plays a vital role in the regulation of intracellular iron homeostasis as well as regulating systemic iron availability. As is the case for other aspects of iron homeostasis, hypoxia significantly modulates the function of the hepcidin/ferroportin pathway in the heart.

NOVEMBER

In November, the Hypoxia meeting mini-reviews start with an exploration of inflammation and adenosine, the role of hypoxia on gut inflammation, and the control of those processes by HIF. Bowser et al. (4) review the latest work on the central role of HIF-driven adenosine metabolism and signaling that is central to providing wide-ranging tissue protection during inflammation in myocardial injury, inflammatory bowel disease and acute lung injury. Colgan and Campbell (8) provide insight into how active HIF-mediated responses to the normal low basal O₂ levels in the gut play key roles in the response to active inflammation. And taking a deeper look, Fagundes and Taylor (11) expand on the effects of hypoxia in the gut and the consequences of enhanced HIF activity on tissue function and disease progression.

The November reviews wrap up with some classic physiology, exploring recent advances in peripheral and central oxygen sensing. Although the carotid bodies are essential in regulating breathing in hypoxia to maintain O₂ homeostasis and survival, the mechanism(s) by which hypoxia stimulates carotid body sensory activity remain controversial. Chang (7) provides a clear review of two discrete models that argue for the seat of O₂ sensing to lie either in the plasma membrane or mitochondria of carotid body cells. Gourine and Funk (14) in their review present a new concept of oxygen sensing and the hypoxic ventilatory response (HVR), traditionally thought to be confined to peripheral chemoreceptors. They examine experimental evidence from animal and human studies and suggest that the lower brainstem contains functional oxygen sensitive elements capable of stimulating respiratory activity independently of peripheral chemoreceptor input. Hypoxic cerebral vasodilation is a highly conserved physiological response coupling cerebral O₂ delivery to metabolic demand, with increasingly important roles identified for the RBC (sensor) and nitric oxide (effector). Beaudin et al. (1) provide a topical review of the basic mechanisms of cerebrovascular regulation in humans in both normoxia, acute and intermittent hypoxia, and the potential alterations in chronic obstructive lung disease and obstructive sleep apnea.

DECEMBER

Oxygen sensing has to precede an organism's response to hypoxia. A vast literature informs us on varied sensors and their mechanisms, but new developments continue to emerge. Two of the most important responses to hypoxia are hypoxic pulmonary vasoconstriction (HPV) and the HVR. Two mini-reviews address the mechanisms by which the pulmonary circulation senses and responds to alveolar hypoxia. In the December issue, Strielkov et al. (31) focus on the

conventional view of the pulmonary artery smooth muscle cell (PASMC) as both sensor and effector of HPV, offering new insights into the role of ROS from Complex III of the electron transport chain in oxygen sensing at Complex IV, and examining the importance of arachidonic acid metabolites and multiple membrane channels, including voltage-dependent potassium, TRPC6 and TRPV4 channels to effect vasoconstriction. Grimmer and Kuebler offer (15) provide an alternative view, arguing that the O₂ sensor must be in the gas-exchanging areas of the lung, in the endothelium, and the hypoxic signal transmitted upstream to the PASMC. They summarize evidence for endothelial-smooth muscle cross-talk that involves connexin 40, epoxyeicosatrienoic acids, sphingolipids, and cystic fibrosis transmembrane conductance regulator. Both reviews offer new ideas for therapeutic targets in patients with impaired HPV, such as sepsis, pneumonia and cystic fibrosis. Despite the clinical importance of pulmonary hypertension (PH), research on the impacts of going to high altitude, or of supplemental O₂ at low altitude in these patients is scant. Interestingly, Ulrich et al. (33) review the available evidence that breathing supplemental O₂ enhances exercise performance at low altitude in both healthy persons and those with PH. While supplemental O₂ will improve exercise at high altitude in the healthy, this has not been studied in PH. The understanding of the physiologic mechanisms will help to counsel individuals planning altitude or air travel and to prescribe O₂ therapy to patients with PH and other hypoxemic disorders.

Related to some aspects of chronic sustained hypoxemia, neocytolysis is the biological process that corrects polycythemia by transient, preferential destruction of young RBCs after normoxia is restored. Song et al. (30) review the evidence that neocytolysis is caused by excessive mitochondrial-derived ROS in reticulocytes, mediated by down-regulation of HIF-controlled

BNIP3L regulated mitophagy and a decrease in RBC antioxidant catalase in hypoxia-produced erythrocytes. Although <1% of patients with obstructive sleep apnea (a form of chronic intermittent hypoxia) are reported to develop polycythemia, increased ROS and mitochondrial mass with decreased RBC antioxidant catalase and BNIP3L in blood cells, along with increased inflammatory markers, are apparent in these patients.

Evidence continues to mount for beneficial effects of hypoxic exposure in certain conditions in various organisms and tissues. Kimura et al. (17) in a succinct review share their recent work on regeneration of damaged myocardium in rats via controlled hypoxic exposure. They have shown that reducing O₂ metabolism in the adult mammalian heart through hypoxic exposure reduces oxidative stress and initiates cardiomyocyte cell cycle re-entry, resulting in cardiomyocyte proliferation and repair of injured myocardium. This remarkable finding may have implications for the deadly problem of heart failure. And in the final invited mini-review from the Hypoxia meeting, Wagner (34) integrates evidence from Operation Everest II and physiological studies of elite climbers for a positive and important role for enhanced muscle capillarity improving performance at extreme high altitudes.

In summary, we believe this series of mini-reviews and research articles will stimulate further investigations and collaborations for a broad range of scientists interested in hypoxia.

Elucidation of mechanistic and translational relationships is paramount to our comprehension of myriad pathologies associated with arterial hypoxemia (e.g., sleep apnea, chronic lung diseases, heart failure) and/or alterations in blood viscosity or hemoglobin levels (e.g., anemic or polycythemic pathologies). Many animals and some highland human populations have

physiological and genetic adaptations that enable their successful existence in a hypoxic environment. Uncovering the molecular basis of hypoxic adaptation will both inform understanding of hematological and other adaptations involved in hypoxia tolerance and form the basis of novel methods of treating conditions of pathological hypoxemia. Continuing fieldwork in high altitude residents is urgent since modernization and migration are changing the traditional ways of life and patterns of exposure to the environment among highlanders everywhere. 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 and adaptation to hypoxia. Supporting and facilitating collaboration to address this paradigm will continue to be the purpose of the International Hypoxia Symposia and of Highlighted Topics such as these published in the *Journal of Applied Physiology*.

161 FIGURE LEGEND

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163 Figure. Illustration of the impact and integration of hypoxia from the 18 invited mini-reviews
164 from Translation in Progress: Hypoxia 2017. Adapted from Sonveaux P, Lobysheva II, Feron O,
165 McMahon TJ. Transport and peripheral bioactivities of nitrogen oxides carried by red blood cell
166 hemoglobin: Role in oxygen delivery. *Physiology* 22: 97-112, 2007

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169 **REFERENCES**

- 170 1. **Beaudin AE, Hartmann SE, Pun M, Poulin MJ.** Human cerebral blood flow control
171 during hypoxia: Focus on chronic pulmonary obstructive disease (COPD) and obstructive
172 sleep apnea (OSA). *J Appl Physiol (1985)* jap.00352.2017, 2017.
- 173 2. **Beidleman BA, Fulco CS, Cadarette BS, Cymerman A, Buller MJ, Salgado RM, Posch**
174 **AM, Staab JE, Sils IV, Yurkevicius BR, Luippold AJ, Welles AP, Muza SR.** Is
175 normobaric hypoxia an effective treatment for sustaining previously acquired altitude
176 acclimatization? *J Appl Physiol (1985)* jap.00344.2017, 2017.
- 177 3. **Berger MM, Macholz F, Lehmann L, Dankl D, Hochreiter M, Bacher B, Bartsch P,**
178 **Mairbaurl H.** Remote ischemic preconditioning does not prevent acute mountain sickness
179 after rapid ascent to 3450 m. *J Appl Physiol (1985)* jap.00505.2017, 2017.
- 180 4. **Bowser JL, Lee JW, Yuan X, Eltzschig HK.** The hypoxia-adenosine link during
181 inflammation. *J Appl Physiol (1985)* jap.00101.2017, 2017.
- 182 5. **Brauner CJ, Harter TS.** Beyond just hemoglobin: Red blood cell potentiation of
183 hemoglobin-oxygen unloading in fish. *J Appl Physiol (1985)* jap.00114.2017, 2017.
- 184 6. **Casillan AJ, Chao J, Wood JG, Gonzalez NC.** Acclimatization of the systemic
185 microcirculation to alveolar hypoxia is mediated by iNOS-dependent increased nitric oxide
186 availability. *J Appl Physiol (1985)* jap.00322.2016, 2017.
- 187 7. **Chang AJ.** Acute oxygen sensing by the carotid body: From mitochondria to plasma
188 membrane. *J Appl Physiol (1985)* jap.00398.2017, 2017.
- 189 8. **Colgan SP, Campbell EL.** Oxygen metabolism and innate immune responses in the gut. *J*
190 *Appl Physiol (1985)* jap.00113.2017, 2017.

- 191 9. **El-Chami M, Sudan S, Lin H-S, Mateika J.** Exposure to intermittent hypoxia and sustained
192 hypercapnia reduces therapeutic CPAP in participants with obstructive sleep apnea. *J Appl*
193 *Physiol* (1985) japplphysiol.00204.2017, 2017.
- 194 10. **Fago A.** Functional roles of globin proteins in hypoxia-tolerant ectothermic vertebrates. *J*
195 *Appl Physiol* (1985) jap.00104.2017, 2017.
- 196 11. **Fagundes RR, Taylor CT.** Determinants of hypoxia inducible factor (HIF) activity in the
197 intestinal mucosa. *J Appl Physiol* (1985) jap.00203.2017, 2017.
- 198 12. **Fluck D, Morris LE, Niroula S, Tallon CM, Sherpa KT, Stembridge M, Ainslie PN,**
199 **McManus AM.** UBC-Nepal expedition: Markedly lower cerebral blood flow in high altitude
200 sherpa children compared to children residing at sea-level. *J Appl Physiol* (1985)
201 jap.00292.2017, 2017.
- 202 13. **Foss JL, Constantini K, Mickleborough TD, Chapman RF.** Short-term arrival strategies
203 for endurance exercise performance at moderate altitude. *J Appl Physiol* (1985)
204 jap.00314.2017, 2017.
- 205 14. **Gourine AV, Funk GD.** On the existence of a central respiratory oxygen sensor. *J Appl*
206 *Physiol* (1985) jap.00194.2017, 2017.
- 207 15. **Grimmer B, Kuebler W.** The endothelium in hypoxic pulmonary vasoconstriction. *J Appl*
208 *Physiol* (1985) japplphysiol.00120.2017, 2017.
- 209 16. **Hsia C.** Drowning in a river with an average depth of three feet: Interpreting athletic
210 performance gains. *J Appl Physiol* (1985) doi: 10.1152/japplphysiol.00733.2017, 2017.
- 211 17. **Kimura W, Nakada Y, Sadek HA.** Hypoxia induced myocardial regeneration. *J Appl*
212 *Physiol* (1985) jap.00328.2017, 2017.

18. **Laguë S.** High-altitude champions: Birds that live and migrate at altitude. *J Appl Physiol* (1985) doi: 10.1152/japphysiol.00110.2017, 2017.
19. **Lakhal-Littleton S, Robbins PA.** The interplay between iron and oxygen homeostasis with a particular focus on the heart. *J Appl Physiol* (1985) jap.00237.2017, 2017.
20. **Morales-Alamo D, Guerra B, Ponce-Gonzalez JG, Guadalupe-Grau A, Santana A, Martin-Rincon M, Gelabert-Rebato M, Cadeffau JA, Cusso R, Dorado C, Calbet JAL.** Skeletal muscle signaling, metabolism and performance during sprint exercise in severe acute hypoxia after the ingestion of antioxidants. *J Appl Physiol* (1985) jap.00384.2017, 2017.
21. **Nakata H, Miyamoto T, Ogoh S, Kakigi R, Shibasaki M.** Effects of acute hypoxia on human cognitive processing: A study using ERPs and SEPs. *J Appl Physiol* (1985) jap.00348.2017, 2017.
22. **Ottestad W, Hansen T, Pradhan G, Stepanek J, Høiseth L, Kåsin J.** Acute hypoxia in a simulated high altitude airdrop scenario due to oxygen system failure. *J Appl Physiol* (1985) doi: 10.1152/japphysiol.00169.2017, 2017.
23. **Roach RC, Wagner PD, Hackett PH.** Translation in progress: Hypoxia. *J Appl Physiol* (1985) 116: 835-836, 2014.
24. **Roach RC, Wagner PD, Kayser B, Hackett PH.** Translation in progress: Hypoxia 2015. *J Appl Physiol* (1985) 119: 1127-1128, 2015.
25. **Rossetti GMK, Macdonald JH, Wylie LJ, Little SJ, Newton V, Wood B, Hawkins KA, Beddoe R, Davies HE, Oliver SJ.** Dietary nitrate supplementation increases acute mountain sickness severity and sense of effort during hypoxic exercise. *J Appl Physiol* (1985) jap.00293.2017, 2017.

- 235 26. **Siebenmann C, Robach P, Lundby C.** Regulation of blood volume in lowlanders exposed
236 to high altitude. *J Appl Physiol (1985)* jap.00118.02017, 2017.
- 237 27. **Sieck GC.** Highlighted topic: Pulmonary circulation and hypoxia. *J Appl Physiol (1985)* 98:
238 1-2, 2004.
- 239 28. **Sieck GC.** Highlighted topics series: Hypoxia influence on gene expression. *J Appl Physiol*
240 *(1985)* 88: 1153-1154, 2000.
- 241 29. **Smith ZM, Krizay E, Sa RC, Li ET, Scadeng M, Powell FL, Jr., Dubowitz DJ.** Evidence
242 from high altitude acclimatization for an integrated cerebrovascular and ventilatory
243 hypercapnic response, but different responses to hypoxia. *J Appl Physiol (1985)*
244 jap.00341.2017, 2017.
- 245 30. **Song J, Sundar K, Gangaraju R, Prchal JT.** Regulation of erythropoiesis after normoxic
246 return from chronic sustained and intermittent hypoxia. *J Appl Physiol (1985)*
247 jap.00119.2017, 2017.
- 248 31. **Strielkov I, Pak O, Sommer N, Weissmann N.** Recent advances in oxygen sensing and
249 signal transduction in hypoxic pulmonary vasoconstriction. *J Appl Physiol (1985)*
250 jap.00103.2017, 2017.
- 251 32. **Sun K, Liu H, Song A, Manalo JM, D'Alessandro A, Hansen KC, Kellems RE, Eltzschig**
252 **HK, Blackburn MR, Roach RC, Xia Y.** Erythrocyte purinergic signaling components
253 underlie hypoxia adaptation. *J Appl Physiol (1985)* jap.00155.2017, 2017.
- 254 33. **Ulrich S, Schneider SR, Bloch KE.** Effect of hypoxia and hyperoxia on exercise
255 performance in healthy individuals and in patients with pulmonary hypertension: A
256 systematic review. *J Appl Physiol (1985)* jap.00186.2017, 2017.

257 34. **Wagner PD.** Operation Everest II and the 1978 Habeler/Messner ascent of Everest without
258 bottled O₂: What might they have in common? *J Appl Physiol* (1985) jap.00140.2017, 2017.

259