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Review

Oxygen in demand: How oxygen has shaped vertebrate physiology ☆

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ABSTRACT

In response to varying environmental and physiological challenges, vertebrates have evolved complex and often overlapping systems. These systems detect changes in environmental oxygen availability and respond by increasing oxygen supply to the tissues and/or by decreasing oxygen demand at the cellular level. This suite of responses is termed the oxygen transport cascade and is comprised of several components. These components include 1) chemosensory detectors that sense changes in oxygen, carbon dioxide, and pH in the blood, and initiate changes in 2) ventilation and 3) cardiac work, thereby altering the rate of oxygen delivery to, and carbon dioxide clearance from, the tissues. In addition, changes in 4) cellular and systemic metabolism alters tissue-level metabolic demand. Thus the need for oxygen can be managed locally when increasing oxygen supply is not sufficient or possible. Together, these mechanisms provide a spectrum of responses that facilitate the maintenance of systemic oxygen homeostasis in the face of environmental hypoxia or physiological oxygen depletion (i.e. due to exercise or disease). Bill Milsom has dedicated his career to the study of these responses across phylogenies, repeatedly demonstrating the power of applying the comparative approach to physiological questions. The focus of this review is to discuss the anatomy, signalling pathways, and mechanics of each step of the oxygen transport cascade from the perspective of a Milsomite. That is, by taking into account the developmental, physiological, and evolutionary components of questions related to oxygen transport. We also highlight examples of some of the remarkable species that have captured Bill's attention through their unique adaptations in multiple components of the oxygen transport cascade, which allow them to achieve astounding physiological feats. Bill's research examining the oxygen transport cascade has provided important insight and leadership to the study of the diverse suite of adaptations that maintain cellular oxygen content across vertebrate taxa, which underscores the value of the comparative approach to the study of physiological systems.

Contents

Abbreviations: 5-HT, serotonin; ACh, acetylcholine; ACR, air convection requirement; CO, carbon monoxide; Co_2, oxygen content; COX, cytochrome C oxidase; E, expiration; EDV, end diastolic volume; ePF, embryonic parafacial respiratory group; ERV, expiratory reserve volume; ESV, end systolic volume; ETC, electron transport chain; f_H, heart rate; f_R, breathing frequency; H_2S, hydrogen sulfide; Hb, hemoglobin; HMR, hypoxic metabolic response; HVR, hypoxic ventilatory response; I, inspiration; LCT, lower critical temperature; MAP, mean arterial pressure; NEC, neuroepithelial cells; NO, nitric oxide; NOS, nitric oxide synthase; P_{50}, partial pressure of oxygen at which Hb is 50% saturated; P_aO_2, arterial oxygen tension; Po_2 or Pco_2, oxygen or carbon dioxide tension; pFRG, para-facial respiratory group; preBötC, pre-Bötzinger Complex; $\dot{Q}$, cardiac output; ROS, reactive oxygen species; Ta, ambient temperature; Tb, body temperature; Tb_{set}, thermoregulatory set point; TNZ, thermoneutral zone; TPR, total peripheral resistance; UCT, upper critical temperature; V_S, stroke volume; V^T, tidal volume.

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1. Foreword

Bill Milsom has dedicated his career to studying adaptations to varying levels of oxygen. The product of an unparalleled comparative pedigree, Bill has had the great fortune of working alongside many of the other leading comparative physiologists of his day. Bill's work has spanned an astoundingly broad swath of species, developmental stages, physiological systems, and corners of the globe. Although the breadth of Bill's investigations is evident from the studies discussed in this very special issue, his interests are broadly centred on the control of breathing, using species differences and ontogeny to determine the neural basis of respiratory pattern formation and the manner in which this has been shaped by evolution to meet the demands of animals living in extreme environments. Bill's approach to science and life is similar and perhaps best characterized by an unending passion and curiosity that has not been blunted by time. Bill is always up for an expedition, a conference, or an experiment. Following a long day of science in the lab or at a conference he will stay up later than students a third his age, drink most of them under the table, and then be in the lab or lecture hall earlier than they can contemplate, fully recharged and ready to do it all again. Bill has an amazing ability to keenly get to the heart of any scientific problem, which is perhaps best characterized by his knack for sleeping through any presentation only to ask insightful questions at the end. Clearly the “Milsom-nod” has amazing regenerative capacity!

As a researcher, Bill has made many notable contributions to physiology. However, as remarkable as his scientific achievements are, if asked, Bill will always cite the successes of his many excellent trainees as his greatest achievement; his many awards for excellence in mentorship as his most cherished recognitions. As a mentor, Bill achieves a careful balance between encouraging and challenging his students, valuing both hard work and play, and providing help to the mentee in the present while encouraging them to dream about the future.

Indeed, Bill has been an inspiring mentor to each of the authors of this paper and his academic progeny populate the faculties of universities across the globe. Therefore, it is with considerable pleasure that we, the final brood of Milsomites, contribute this review of physiological responses to hypoxia in his honour.

2. Introduction

The primary function of the cardio-respiratory system is to extract oxygen from the atmosphere and deliver it to the mitochondria of cells. At the cellular level, mitochondria utilize oxygen as the terminal electron acceptor to produce ATP through the electron transport chain (ETC) via the biochemical process of oxidative phosphorylation. Together, the series of physiological events that connects environmental oxygen to cellular metabolism is termed the oxygen transport cascade (Fig. 1). This cascade is composed of four primary steps: ventilation, diffusion of oxygen from the air into the blood, circulation, and diffusion of oxygen from the blood into the cells. At sea level, oxygen makes up ~20% of inspired air (~160 Torr), but at each step of the oxygen transport cascade this percentage becomes markedly reduced, such that at the cellular level the oxygen tension (P_{O_2}) may be as low as ~5 Torr (Weibel, 1984; di Prampero, 1985). Maintaining this gradient is essential to the function of the oxygen transport cascade as the diffusion of oxygen from the atmosphere into the blood, and from the blood into the tissues, is a passive process. Nonetheless, despite the relatively low oxygen saturation at the tissue level in normoxia, there is still abundant oxygen for the mitochondrial synthesis of sufficient ATP to meet cellular energy requirements.

During periods of hypoxia, however, oxygen availability becomes limited, oxidative phosphorylation is impaired, and metabolic throughput along the ETC is greatly decreased. Hypoxemia (i.e. hypoxia of the blood) occurs due to a variety of factors, including reduced environmental oxygen availability, physical exercise, disease, or a combination of these. Indeed, hypoxic environments are common on Earth and many animals inhabit such regions and perform some or all of their daily activities or life cycle functions in varying or low oxygen (Bickler and Buck, 2007). For example, many animals are adapted to life at high-altitude, where ambient oxygen levels are reduced relative to sea level due to lower barometric pressure (see Section 7). These animals must develop, reproduce, and exercise in hypoxia, and this challenge has driven the evolution of a variety of adaptations that enhance oxygen delivery at various stages of the oxygen transport cascade and/or reduce metabolic demand at the cellular level. These adaptations mitigate the impact of reduced environmental oxygen availability by enhancing its delivery through the body, or in situations where enhanced delivery is not sufficient, by reducing the need for oxygen to generate cellular energy at the tissue level (i.e. by decreasing metabolism).

Common adaptations in the oxygen transport cascade include changes in the sensitivity of chemosensory cells and organs to hypoxia, alterations in the anatomy, mechanics, and neural/cellular control of ventilation and cardiac function, biochemical changes to the oxygen carrying capacity of the blood, anatomical adjustments that alter the diffusion distance across which gases must travel between the blood and tissues (and *vice versa*), and systemic adaptations that minimize energy demand, either through reduced behaviours (i.e. torpor or hibernation), shutting down non-essential tissues to preserve energy for oxygen-