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Review

Control of breathing and the circulation in high-altitude mammals and birds ☆

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ABSTRACT

Hypoxia is an unremitting stressor at high altitudes that places a premium on oxygen transport by the respiratory and cardiovascular systems. Phenotypic plasticity and genotypic adaptation at various steps in the O_2 cascade could help offset the effects of hypoxia on cellular O_2 supply in high-altitude natives. In this review, we will discuss the unique mechanisms by which ventilation, cardiac output, and blood flow are controlled in high-altitude mammals and birds. Acclimatization to high altitudes leads to some changes in respiratory and cardiovascular control that increase O_2 transport in hypoxia (e.g., ventilatory acclimatization to hypoxia). However, acclimatization or development in hypoxia can also modify cardiorespiratory control in ways that are maladaptive for O_2 transport. Hypoxia responses that arose as short-term solutions to O_2 deprivation (e.g., peripheral vasoconstriction) or regional variation in O_2 levels in the lungs (i.e., hypoxic pulmonary vasoconstriction) are detrimental at in chronic high-altitude hypoxia. Evolved changes in cardiorespiratory control have arisen in many high-altitude taxa, including increases in effective ventilation, attenuation of hypoxic pulmonary vasoconstriction, and changes in catecholamine sensitivity of the heart and systemic vasculature. Parallel evolution of some of these changes in independent highland lineages supports their adaptive significance. Much less is known about the genomic bases and potential interactive effects of adaptation, acclimatization, developmental plasticity, and trans-generational epigenetic transfer on cardiorespiratory control. Future work to understand these various influences on breathing and circulation in high-altitude natives will help elucidate how complex physiological systems can be pushed to their limits to maintain cellular function in hypoxia.

Contents

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1. Introduction

High-altitude environments pose multiple challenges to the organisms that inhabit them, including cold temperatures, low humidity, and hypobaric hypoxia. Unlike temperature and humidity, which can fluctuate daily and seasonally, the low partial pressure of oxygen (PO_2) at high altitude is unavoidable and unremitting. For example, many high-altitude human and mammal populations live, grow, and reproduce at over 4,000 m elevation where the PO_2 is roughly 60% of that at sea level. Some birds are known to fly at higher altitudes as a part of their natural migration, despite the fact that flight is an oxygen demanding process that becomes all the more challenging in a hypoxic environment (Ward et al., 2002; Hawkes et al., 2013). This implies that of the two general strategies for coping with hypoxia – reduction of oxygen demands by metabolic depression (Boutilier, 2001) and/or increases in the supply of oxygen through transport pathways (Hochachka, 1986) – only the latter is a feasible option for the survival and fitness of animals native to high altitude.

Performance in high-altitude hypoxia is enhanced by increases in the capacity to transport oxygen along the oxygen cascade, comprised of ventilation, pulmonary oxygen diffusion, circulation of oxygen in the blood, and tissue oxygen diffusion and utilization (Fig. 1). This could foreseeably be achieved through phenotypic plasticity – responses to high-altitude exposure that occur within the lifetime of an individual – or evolved heritable (e.g., genetic) changes that modify the capacity for oxygen transport at steps in the cascade. Although the term 'adaptation' can often be used in both contexts, we will restrict its use to traits that evolved by natural selection. The highland phenotype – arising through adaptation or various mechanisms of phenotypic plasticity – can include changes in many morphological traits that enhance the capacity for oxygen diffusion, including increases in the surface area of the pulmonary air-blood interface (Hsia et al., 2005, 2007; Ravikumar et al., 2009; Scott et al., 2011), increases in the capillarity of peripheral tissues (León-Velarde et al., 1993; Mathieu-Costello et al., 1998; Scott et al., 2009), and a redistribution of mitochondria towards capillaries to a subsarcolemmal location in the skeletal muscle (Scott et al., 2009). The highland phenotype can also differ from that of lowlanders in how the blood binds O_2, mediated by evolved and acclimatization-induced changes in haemoglobin concentration and/or haemoglobin-O_2 affinity (Monge and León-Velarde, 1991; Nikinmaa, 2001; Weber and Fago, 2004; Storz and Moriyama, 2008). These components of the highland phenotype are extremely important at high altitudes, and have been well reviewed elsewhere (Monge and León-Velarde, 1991; Storz et al., 2010; Scott, 2011). In the spirit of celebrating the impressive career of Bill Milsom, our attention on the unique physiology of high-altitude animals will focus on the mechanisms that control breathing and the circulation in hypoxia – a topic that is near and dear to Bill's heart and to which he has devoted a great deal of attention. We write this article with deep-felt thanks to Bill for many years of inspiring research and for being a true ambassador of comparative physiology.

2. Phenotypic plasticity and high-altitude hypoxia

The response to high-altitude hypoxia in lowland animals provides insight into whether phenotypic plasticity can generally be regarded to facilitate or impede evolutionary adaptation in animals that colonize high altitudes (Storz et al., 2010). Many rapid physiological responses to hypoxia in adult animals occur within minutes to hours of acute exposure, which can be subsequently modulated by adjustments in control systems after longer durations of chronic acclimatization to hypoxia. Hypoxia exposure during prenatal and postnatal development can have life-long persistent effects that differ substantially from the hypoxia responses observed in adults (Bavis, 2005). Parental exposure to hypoxia may even have long-lasting consequences that are transmitted to offspring by epigenetic mechanisms, akin to trans-generational plasticity, but we are only just beginning to understand how parental effects can influence respiratory and cardiovascular physiology (Ho and Burggren, 2010).

2.1. Responses of adult lowlanders to high-altitude hypoxia

2.1.1. The hypoxic ventilatory response

The hypoxic ventilatory response (HVR) is initiated within one breath of a reduction in arterial PO_2, and involves an increase in breathing that helps maintain O_2 transport (Powell et al., 1998; Brutsaert, 2007). The carotid body immediately senses the drop in arterial PO_2 and stimulates afferent sensory discharge in the carotid sinus nerve

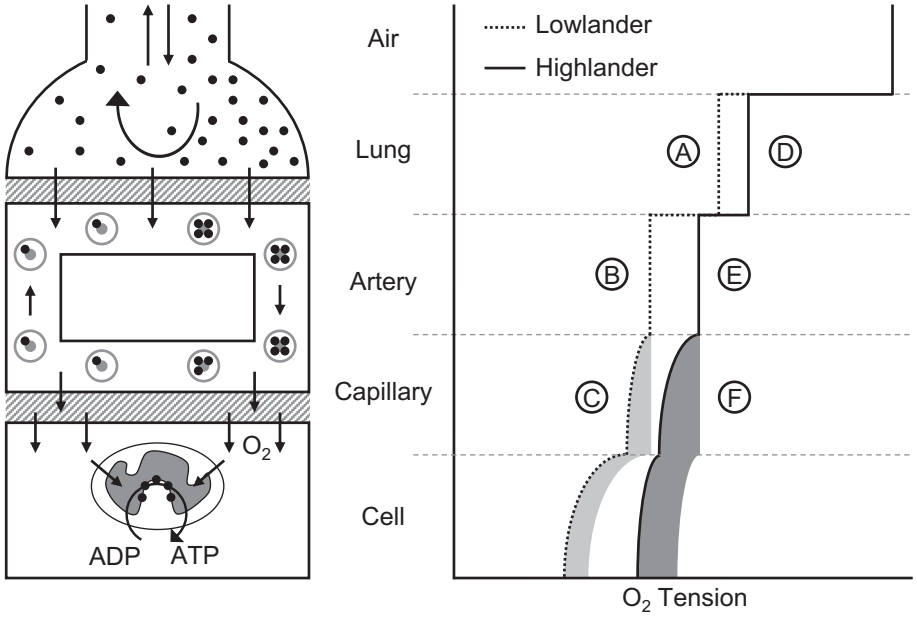

Fig. 1. The oxygen cascade – oxygen tension (PO_2) at each step in the pathway could be increased in high-altitude natives by genotypic adaptation and/or phenotypic plasticity. PO_2 declines along the length of capillaries as O_2 diffuses into target tissues, so a range of capillary PO_2 drives diffusion into tissues. PO_2 also declines with distance from capillaries, so there should be a range of cellular PO_2 depending on both capillary PO_2 and diffusion distance. Adapted from (Taylor and Weibel, 1981) and (Scott, 2011).