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Evolved Mechanisms of Aerobic Performance and Hypoxia Resistance in High-Altitude Natives

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Abstract

Comparative physiology studies of high-altitude species provide an exceptional opportunity to understand naturally evolved mechanisms of hypoxia resistance. Aerobic capacity (VO_2max) is a critical performance trait under positive selection in some high-altitude taxa, and several high-altitude natives have evolved to resist the depressive effects of hypoxia on VO_2max. This is associated with enhanced flux capacity through the O_2 transport cascade and attenuation of the maladaptive responses to chronic hypoxia that can impair O_2 transport. Some highlanders exhibit elevated rates of carbohydrate oxidation during exercise, taking advantage of its high ATP yield per mole of O_2. Certain highland native animals have also evolved more oxidative muscles and can sustain high rates of lipid oxidation to support thermogenesis. The underlying mechanisms include regulatory adjustments of metabolic pathways and to gene expression networks. Therefore, the evolution of hypoxia resistance in high-altitude natives involves integrated functional changes in the pathways for O_2 and substrate delivery and utilization by mitochondria.

INTRODUCTION

Aerobic scope: the calculated difference between VO_2max and BMR or the aerobic metabolism available above maintenance costs

High-altitude environments pose considerable physiological challenges compared to those at sea level. A progressive reduction in atmospheric pressure occurs with the ascent to high elevations, resulting in hypobaric hypoxia and a concomitant decline in the partial pressure of oxygen (PO_2). In fact, at an altitude of 4,000 m, each breath contains only 60% of the O_2 that is available at sea level. This reduction in O_2 availability in high-altitude environments threatens aerobic metabolism and poses a major challenge to maintaining an acceptable aerobic scope for activity (1) (**Figure 1**), and the ability of highland animals to survive and perform in these harsh conditions has long fascinated scientists. Early observations on lowland humans defined most of the more dramatic ill effects of this environment by the 1800s (2). By the 1920s, research on highland native populations had begun, and for almost a century the field of high-altitude physiology has been dominated by studies on humans (3). The long-term residence of human populations above 4,000 m on three continents for hundreds of generations was likely sufficient time for the selection of genetic variants favoring survival and performance in hypoxia (4–6), and in recent years, there has been renewed vigor in the field as evidence for the genetic basis of high-altitude adaptation emerges (7–9).

Alpine environments are also home to a diversity of animal species (10, 11). Interest in comparative physiology of these highland taxa has surfaced periodically (e.g., 3, 12, 13) but with more sustained intensity over the last few decades (see 14–18). Indeed, the study of these highland animal taxa provides an excellent way to understand the evolution of complex physiological systems that underlies adaptive variation in organismal performance.

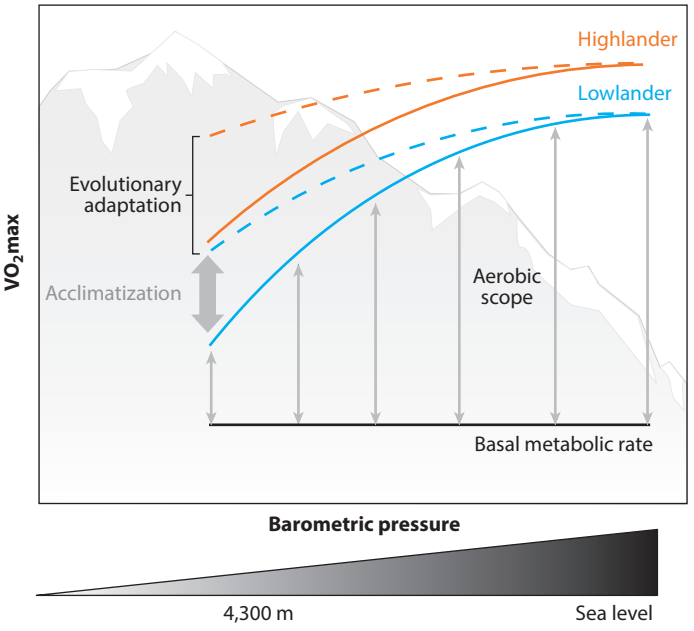


Figure 1

Aerobic performance at high altitude results from evolved differences and acclimatization. Maximum oxygen consumption (VO_2max) declines with oxygen availability, as inspired partial pressure of oxygen (PO_2) is reduced as barometric pressure declines with increasing altitude. Highlander deer mice have evolved a higher VO_2max than lowlander deer mice at sea-level PO_2 and in the PO_2 at 4,300 m altitude (difference between *orange* and *blue lines* signifies evolutionary adaptation). This is overlaid by environmentally induced plasticity (acclimatization) in aerobic performance (difference between *solid* and *dotted lines*), which allows highlander mice to almost fully compensate for reduced O_2 availability at altitude. Based on data from References 21, 27, and 33.

Hypoxia is an unavoidable and unremitting stressor in the high alpine, but it is not the only challenge facing animals in these environments. Ambient temperatures can decrease with altitude at a rate of approximately 6.5°C for every 1,000 m in elevation. Therefore, high-altitude regions are generally colder than low-altitude regions at the same latitude. For example, at 3,800 m in the White Mountains of California, the average nighttime temperature in June is 12–14°C cooler than similar latitudes at low altitude at that time of year (15, 19). These conditions can be challenging for many animals, especially small endothermic mammals and birds. As body size decreases, the surface area over which heat is lost increases relative to the volume of tissue available for heat production. Small mammals also have a limited capacity for insulation as either fat or fur compared to animals of larger body size (20). Therefore, for many small species, the temperatures at high altitude are continuously below their thermoneutral zone—the narrow range of ambient temperatures where body temperature can be maintained solely using basal metabolic rates (BMRs). As such, small endotherms at high altitude are challenged with high demands for thermogenesis, likely contributing to their very high daily energy expenditures (15), and possibly restricting the aerobic scope available for activity.

This review examines the evolved mechanisms of hypoxia resistance that allow animals from high altitude to survive and thrive in their harsh native environment. A number of animals are known to reside at high altitude, including several small rodent species. One of the most extensively characterized is the North American deer mouse (*Peromyscus maniculatus*), which remains active year-round in the cold alpine, and therefore requires significant aerobic capacity for sustained heat generation in hypoxia. Recently, our laboratories, as well as others (e.g., 21–27), have begun to elucidate the evolved physiological mechanisms of hypoxia resistance in high-altitude natives of this species and others. We discuss the relative roles of genetic specialization and environmentally induced plasticity on the processes underlying aerobic metabolism, with a focus on pathways for O_2 and substrate delivery and their convergence at mitochondria (**Figure 2**).

BMR: basal metabolic rate is O_2 consumption of an animal while resting, postabsorptive, and at ambient temperature within its thermal neutral zone

Aerobic capacity: maximal capacity for O_2 consumption of a tissue or by an organism (here a synonym for VO_2max)

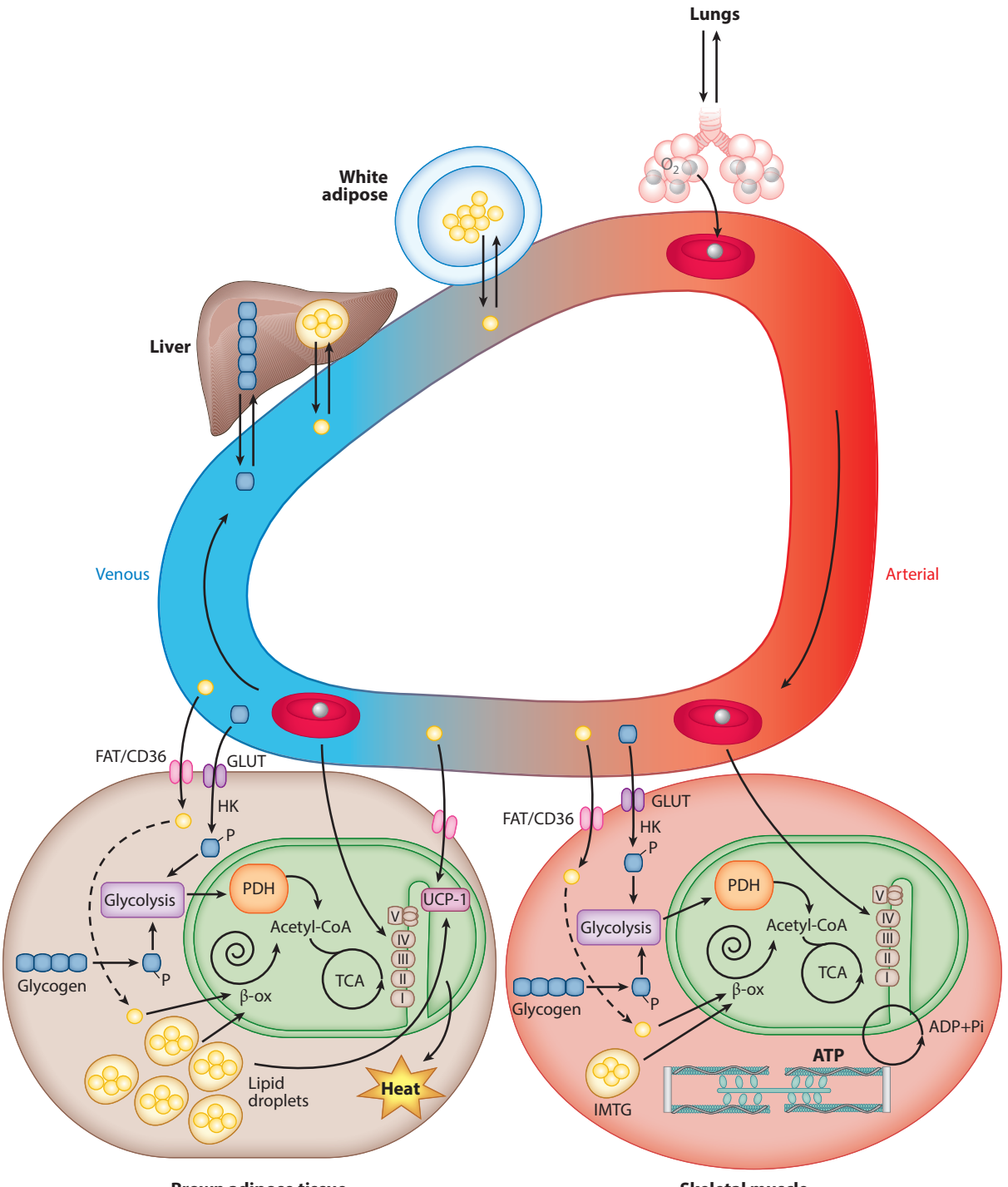
Acclimatization: the collective responses during chronic exposure to altered natural environmental conditions

Acclimation: the collective responses during chronic exposure to an altered environment (typically 1–2 variables) in controlled laboratory conditions

Phenotypic plasticity: the ability of an organism (or genotype) to change its phenotype in response to different environments

Acclimatization, Adaptation, and Physiological Regulation

The ability of high-altitude natives to maintain adequate aerobic performance could result from a combination of evolved genetic specializations, environmentally induced plasticity (i.e., acclimatization, developmental plasticity, etc.), and the interaction between these two processes such as when plasticity evolves (28). A major focus of past high-altitude research has been to identify the mechanisms underlying acclimatization to natural high-altitude environments and acclimation to chronic hypoxia in the laboratory in low-altitude natives (29). For those species that are distributed across a wide range of altitudes, it is predicted that selection may maintain or even promote these forms of phenotypic plasticity, since no single phenotype would be optimal across the full range of environments (28). However, it has often been difficult in past research to distinguish whether high-altitude phenotypes arise from evolved (genetically based) specializations or from phenotypic plasticity, particularly in human studies (8, 30), and we are just beginning to understand how the evolved capacity for plasticity may differ in high-altitude natives. On the one hand, evolved differences in phenotypic plasticity in response to environmental hypoxia may arise from changes in the responsiveness to reductions in tissue O_2 levels. On the other hand, differences in phenotypic plasticity could arise from evolved changes in the capacity for O_2 delivery in environmental hypoxia, thus altering the severity of tissue O_2 deprivation and thus the signal for plasticity at tissues. For example, highland deer mice have evolved a high blood O_2 affinity that appears to facilitate higher O_2 saturations in hypoxia (27, 31, 32). In this example, potential improvements in O_2 delivery to tissues may reduce apparent plasticity in response to environmental hypoxia by restoring tissue O_2, rather than via any evolved changes in the cellular mechanisms of phenotypic plasticity per se.



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Pathways for O_2 and substrate transport and utilization by mitochondria. The transport of O_2 (*gray spheres*) involves ventilation and diffusion from air to blood in the lungs, circulation (arterial, venous) in erythrocytes, diffusion into cells of active tissues, and O_2 utilization by mitochondria. In a postabsorptive state, substrates are supplied to the circulation from the liver and white adipose tissue (lipids, *yellow spheres*; carbohydrates, *blue polygons*). Arrows indicate the direction of transport processes between tissues and blood. Locomotory muscle, which is highly active during exercise and thermogenesis, also contains intracellular stores of glycogen and IMTGs. In this tissue, substrates from the circulation and from intracellular stores provide acetyl-CoA for the TCA cycle, via glycolysis in the cytosol and β-ox and the PDH reaction within mitochondria. This provides reducing equivalents for the electron transport system that supports oxidative phosphorylation, and the ATP produced supports muscle contraction or shivering. In the BAT, electron transport instead supports heat production via UCP-1, stimulated by fatty acids from the circulation or multilocular lipid droplets. Adapted with permission from Reference 40. Abbreviations: ADP, adenosine 5′-diphosphate; BAT, brown adipose tissue; β-ox, β-oxidation; FAT/CD36, fatty acid translocase; GLUT, glucose transporter; HK, hexokinase; IMTG, intramuscular triglyceride; P, phosphorylated; PDH, pyruvate dehydrogenase; Pi, inorganic phosphate; TCA, tricarboxcylic acid; UCP-1, uncoupling protein-1.

The mechanisms responsible for high-altitude adaptation and phenotypic plasticity involve variation in both transcript abundance and regulatory plasticity of physiological systems. Recent studies from our laboratories and others have begun to quantify this variation in the transcriptome and the accompanying variation in phenotypic traits involved in O_2 delivery and utilization pathways in deer mice native to high altitude (21, 25, 26, 33–35). However, variation in systems-level function between high- and low-altitude individuals may not necessarily be solely attributable to differences in transcription. Fluxes through O_2 and substrate pathways, and how they are regulated in response to acute changes in energetic demand, cannot be fully understood from measurements of traits at lower levels of organization. Therefore, it is critical to consider the mechanisms of regulation of protein activity, organelle function, cellular metabolism, and the function of organ systems to fully appreciate the evolved mechanisms of aerobic performance and hypoxia resistance in high-altitude natives. We consider these integrative mechanisms, to the extent that the literature allows, in our discussion below.

What Performance Traits Are Important at High Altitude?

Natural selection acts on organismal performance, loosely defined as how well an individual can carry out a task that is ecologically relevant and that impacts biological function and reproductive success (36). It is a major goal of comparative physiology to uncover the mechanistic basis of adaptive differences in performance (37). Aerobic performance is a particularly pertinent performance trait in the hypoxia at high altitude, because aerobic metabolism is critical for remaining active in the cold and for sustaining locomotion (16, 21). Because hypoxia is both unavoidable and unremitting at high altitude, some short-term mechanisms for coping with O_2 deprivation (e.g., metabolic depression, anaerobic metabolism) are of limited effectiveness, and the ability to maintain aerobic metabolism is critically important. However, hypoxia can have debilitating effects on aerobic performance (**Figure 1**), which can limit locomotor activity or can result in hypothermia by impairing thermogenesis (38). Acclimatization may help compensate for low O_2 availability by adjusting physiological traits that enhance O_2 delivery, but compensation to restore aerobic capacity is partial at best in lowlanders (39). However, full compensation may have evolved in some, if not all, taxa that are native to high altitudes (15; N. Wall, C.E. Robertson, A.E. Schlater, L. Hayward, G.B. McClelland, unpublished observations) (**Figure 1**). There are several aspects of aerobic metabolism that represent relevant performance measures and are possible targets of selection at high altitude.

Maximum oxygen consumption. The upper limits of aerobic metabolism are defined by maximal rates of O_2 consumption (VO_2max), which is generally thought to reflect the capacity for flux through the O_2 transport cascade (40). This trait is often measured as VO_2max during either forced exercise (e.g., on a treadmill or bicycle) or acute cold exposure, referred to here as exercise-induced or cold-induced VO_2max, respectively (8, 22, 25, 27, 39, 41–43). Surprisingly, high-altitude acclimatization does little to improve exercise-induced VO_2max in hypoxia in humans (8, 39, 42). Depending on the study, highland native humans of Tibetan and Andean heritage have been shown to have a higher, similar, or even lower exercise-induced VO_2max than lowlanders when tested and compared in normoxia (reviewed in 4), but highlanders are generally more resistant to the effects of hypoxia on VO_2max (30, 44). Using deer mice of highland and lowland origin that were born and raised in common lab conditions, we have shown that hypoxia acclimation increases exercise-induced VO_2max in hypoxia in both populations. This plasticity is superimposed upon a genetically based increase in hypoxic VO_2max in highlanders compared to lowlanders (25). Similarly, exercise-induced VO_2max in hypoxia is higher in wild highland *Phyllotis xanthopygus* (a species of leaf-eared mouse native to high altitude in the Andes) than in its low-altitude counterparts (*P. amicus* and *P. limatus*), when each is compared after several weeks of acclimation to low-altitude conditions in the laboratory. However, this is not true of highland *P. andium* (22), which may suggest that an elevated hypoxic VO_2max is not a hallmark of high-altitude adaptation in this genus, but it is unknown if these highland species have greater acclimatization responses to their native environments.

Although exercise-induced VO_2max and cold-induced VO_2max are both measures of aerobic capacity, the two traits are not necessarily equivalent in small mammals (reviewed in 45). Cold-induced VO_2max in small placental mammals incorporates the contributions of BMR, shivering thermogenesis (ST) by skeletal muscle, and nonshivering thermogenesis (NST) carried out principally by brown adipose tissue (BAT) (46, 47). Depending on thermal history and altitude ancestry, cold-induced VO_2max may exceed exercise-induced VO_2max (e.g., 48), likely reflecting the stronger selective pressure on thermogenic capacity in smaller animals. This may also reflect differences in the contributions of major O_2-consuming tissues for exercise (skeletal muscle) (49, 50) versus thermogenesis (skeletal muscle and BAT) (17, 51). Changes in cold-induced VO_2max in high-altitude populations could be influenced by changes in any of the sources of heat production (i.e., BMR, ST, and NST) (17). Similar to exercise-induced VO_2max, cold-induced VO_2max in wild highland deer mice is the combined result of environmentally induced plasticity and genetically based increases in hypoxic VO_2max in highlanders compared to lowlanders (33, 52) (**Figure 1**). Acclimation to hypobaric hypoxia or cold, or the combination of cold and hypoxia, increases cold-induced VO_2max in deer mice born and raised in captivity (27; N. Wall, C.E. Robertson, A.E. Schlater, L. Hayward, G.B. McClelland, unpublished observations). Therefore, the combination of chronic cold and hypoxia that can have a negative effect on NST in laboratory mice (53) might presumably be overcome in high-altitude natives. Ongoing work is examining the relative contributions of ST and NST to total heat production and how they might differ between lowland and highland populations of deer mice.

Increases in VO_2max could foreseeably augment aerobic scope in high-altitude natives. Aerobic scope ($VO_2max - BMR$) is the capacity for increasing aerobic metabolism above maintenance costs to support exercise, thermogenesis, and all other aerobic activities. This trait may be somewhat distinct from VO_2max, based on work in lowland mammals suggesting that BMR can covary with VO_2max such that aerobic scope may not vary between taxa even when VO_2max does. However, unlike some others (15, 19), we have observed little evidence for such a relationship between BMR and VO_2max in high-altitude deer mice (N. Wall, C.E. Robertson, A.E. Schlater, L. Hayward,

VO_2max: maximal rates of O_2 consumption induced by exercise or acute cold exposure

O_2 transport cascade: the physiological pathway through which O_2 travels from ambient air to mitochondria

ST: shivering thermogenesis is the process of heat production through the uncoordinated contractions of skeletal muscle in response to cold temperature

NST: nonshivering thermogenesis is an increase in metabolic heat production by chemical means that does not involve muscle contraction

G.B. McClelland, unpublished observations), suggesting that evolved increases in aerobic scope arise from the evolved increases in VO_2max in this taxon.

In order for increases in aerobic capacity to evolve at high altitude, they must improve reproductive success. In a pivotal mark-recapture study of high-altitude populations of deer mice, Hayes & O'Connor (16) showed that higher cold-induced VO_2max increased the probability of surviving in the hypoxic cold of high altitude. Remarkably, biophysical models of heat transfer in this species (54) suggested that the difference between life and death was an ability to withstand environmental temperatures only 1–2°C cooler (16). This directional selection for greater VO_2max at high altitude likely contributed to the population differences in this fitness-related trait that we and others have measured between wild populations of lowland and highland mice (15, 21, 33, 52). In fact, wild deer mice from high altitude appear capable of fully compensating for low environmental PO_2 and have similar cold-induced VO_2max in hypoxia as do wild lowlanders in normoxia (15, 19) (**Figure 1**). It remains unclear whether VO_2max is associated with reproductive success in highland native humans (8) or, to our knowledge, in any other highland animals.

Other indices of aerobic performance. Other indices of aerobic metabolism could be fitness-relevant performance traits that have been targets of selection at high altitude. Fitness at high altitude may be linked to the ability of animals to sustain elevated (but submaximal) rates of metabolism to support activity or thermogenesis over prolonged durations (55). Field metabolic rate (FMR) incorporates the total daily energy use, including BMR, thermoregulatory costs, locomotion, specific dynamic action, reproduction, and immune defense. FMR is elevated in some animals at high altitude, likely because they are continuously at temperatures below their thermal neutral zone, even in the summer. In fact, it has been estimated that highland deer mice operate close to VO_2max for much of the year (15, 19). This may favor the evolution of thermogenic endurance (e.g., the length of time animals are able to maintain >90% of VO_2max) in high-altitude natives (52). However, in studies of deer mice, although thermogenic endurance differs between wild populations of lowland and highland deer mice in their native environments, this difference is almost entirely due to phenotypic plasticity in response to the high-altitude environment (52).

Therefore, the current evidence from several species suggests that high-altitude natives have often evolved to resist the depressive effects of hypoxia on aerobic capacity, but that the evolution of other aerobic performance traits may be idiosyncratic. What mechanisms underlie the evolution of aerobic capacity and its resistance to hypoxia in high-altitude natives? This question has received relatively little attention, and most research has focused on highland human populations, but the emerging evidence from humans and other species points to evolved changes in the pathways for O_2 and substrate delivery and in mitochondrial physiology as the likely mechanisms of hypoxia resistance in high-altitude natives.

THE OXYGEN CASCADE OF HIGH-ALTITUDE NATIVES

Hypoxia depresses aerobic performance in large part because it impairs O_2 delivery to tissues, so how might high-altitude natives compensate for these effects? One might anticipate that increases in the structural and functional capacities for flux through the O_2 transport cascade—ventilation, pulmonary O_2 diffusion, circulation, tissue O_2 diffusion, and mitochondrial O_2 utilization—could help compensate for the effects of environmental hypoxia (**Figure 2**). This could involve increases in capacity at all steps in the cascade (40, 56) or selective changes in a subset of influential steps (57, 58). High-altitude natives might also augment aerobic performance in hypoxia by avoiding some of the maladaptive impacts of chronic hypoxia on respiratory and circulatory function. How have these traits evolved in high-altitude natives to help improve hypoxia resistance? We next address

what is known about the answer to this question, with the exception that we leave our discussion of mitochondrial O_2 utilization until a later section, where we discuss the role of mitochondria in respiration and metabolic fuel oxidation in high-altitude natives.

Flux Capacity of the O_2 Transport Cascade

The morphological capacity of the lungs for O_2 diffusion is augmented in many high-altitude natives. Many studies in humans, other mammals, and birds suggest that highlanders have greater lung volumes and/or surface areas for gas exchange than lowlanders when compared in their native environments (30, 59, 60). However, hypoxia exposure is well known to induce lung growth and remodeling, particularly in early life (25, 61–63). Whether evolved changes in lung structure help further enhance pulmonary O_2 diffusion in high-altitude natives is unclear, with some studies showing evidence for genetically based changes in lung morphology (64, 65), but others do not (30, 66). Nevertheless, hypoxia-induced plasticity in lung structure likely improves O_2 uptake into the blood and thus helps high-altitude natives compensate for the effects of hypoxia on aerobic performance.

Evolved increases in hemoglobin (Hb)-O_2 affinity appear to contribute an added safeguard against arterial hypoxemia in many high-altitude natives. This is particularly evident in birds, in which there is a strong positive relationship between Hb-O_2 affinity and native altitude, and is also true of many (but not all) high-altitude mammals (31, 67). These genetically based changes in Hb function generally involve either an increase in intrinsic O_2-binding affinity or a reduction in the sensitivity to allosteric effectors such as H^+, CO_2, Cl^-, and organic phosphates (68, 69). In some cases, animals that have evolved an increased Hb-O_2 affinity have also been shown to maintain higher arterial O_2 saturation in hypoxia than their lowland counterparts (27, 32, 70). The relative benefit of increased Hb-O_2 affinity alone (in the absence of other potential adaptations for enhancing pulmonary O_2 uptake) is unclear, but it is generally presumed to elevate arterial O_2 saturation during hypoxia in vivo.

The capacity for circulatory O_2 delivery also appears to be enhanced by evolved increases in maximum cardiac output in some high-altitude natives. For example, Tibetan humans achieve higher maximal cardiac outputs and stroke volumes during exercise in hypoxia than do Han Chinese lowlanders, even after lengthy acclimatization, in direct association with greater VO_2max in hypoxia (71, 72). In deer mice, hypoxia acclimation increases heart rate at VO_2max, but high-altitude populations have evolved a greater cardiac O_2 pulse (the quotient of VO_2max and heart rate, which reflects the O_2 extracted from the blood per heartbeat), suggesting that they too maintain higher stroke volumes than their lowland counterparts (27).

The capacity for O_2 diffusion from capillaries into active tissues appears to be augmented in many high-altitude natives. Studies in humans, other mammals, and birds suggest that highlanders have greater capillarity in the skeletal muscle than lowlanders when compared in their native environment (34, 73, 74). In some cases, these differences in muscle capillarity have been shown to persist in comparisons between highlanders and lowlanders raised in common environments (25, 75), suggesting that the differences have a genetic basis. Some high-altitude natives have also evolved higher muscle myoglobin content (66) and a preferential proliferation of subsarcolemmal mitochondria that should reduce intracellular O_2 diffusion distances (75, 76). The mechanisms underlying the differences in muscle capillarity and O_2 transport are not entirely clear, but we and others have shown in deer mice that they are associated with population differences in the expression of genes involved in energy metabolism, muscle development, and vascular development (33, 34), and many genes with roles in angiogenesis and energy metabolism appear to have undergone selection in high-altitude taxa (77–79). These evolved changes in the muscle should increase the

capacity for O_2 extraction from the blood and act concertedly with evolved changes in other steps in the O_2 cascade to increase aerobic performance in hypoxia.

Maladaptive Plasticity of Respiratory and Circulatory System Function

High-altitude natives also appear to have evolved in such a way as to attenuate many of the maladaptive responses to chronic hypoxia. Many responses to high-altitude hypoxia are considered to be forms of maladaptive plasticity because they contribute to high-altitude diseases (e.g., chronic mountain sickness in humans, brisket disease in cattle) (28, 80–83). In humans, it has even been suggested that the harmful impacts of maladaptive plasticity can outweigh the benefits of acclimatization—that humans in hypoxia represent "a conspiracy of maladaptation" (80). The three key examples of maladaptive plasticity in chronic hypoxia that are discussed below can result in significant impairments in O_2 transport, so the attenuation of these responses in high-altitude natives would be expected to improve aerobic performance.

HPH: hypoxic pulmonary hypertension occurs in response to chronic hypoxia, as low PO_2 causes vasoconstriction and smooth muscle proliferation in lung vasculature

***EPAS1*:** gene that encodes for the protein hypoxia-inducible factor (HIF)-2α

Hypoxic pulmonary hypertension (HPH) is one of the most devastating maladaptive responses to chronic hypoxia in lowlanders (80, 84, 85). HPH occurs because pulmonary arteries constrict in response to hypoxia, and then remodel, thicken, and become less distensible over time (84). This constriction of pulmonary vessels is valuable at sea level to direct blood away from poorly ventilated regions of the lung for ventilation-perfusion matching, but it is counterproductive at high altitudes where hypoxia occurs throughout the lungs. HPH can become life threatening because it can impair O_2 uptake and cause pulmonary edema, right-ventricle hypertrophy, and heart failure (85). However, several high-altitude taxa have been shown to exhibit little to no HPH (86–88). High-altitude deer mice do not experience right-ventricle hypertrophy in chronic hypoxia, in contrast to the robust right-ventricle hypertrophy that occurs in low-altitude mice, and this difference occurs in association with the differential expression of genes involved in immune and inflammatory signaling (interferon regulatory factors and their targets) that are known to be involved in cardiac hypertrophy and several cardiometabolic diseases (89, 90).

Many high-altitude natives also blunt the rise in blood hemoglobin content in chronic hypoxia (3, 5, 8, 91, 92). In lowlanders, chronic exposure to hypoxia is well known to increase blood Hb concentration, which is initially mediated by reductions in plasma volume and later followed by erythropoiesis and an expansion in red blood cell volume (93). Erythropoiesis has long been considered a hallmark of acclimatization that helps augment the O_2 concentration in arterial blood. However, it is now considered by many to be maladaptive at high altitudes because it increases blood viscosity, which can decrease cardiac output and O_2 delivery, increase the prevalence of high-altitude diseases, and reduce reproductive success (5, 8, 28, 94). The cellular mechanisms for the evolved blunting of the rise in blood Hb are not well understood, but it may result from selection on genes involved in the hypoxia-inducible factor (HIF) pathway (5), a pathway that is well known to regulate erythropoiesis (95, 96). The gene for HIF-2α (*Epas1*) in particular has undergone selection in several high-altitude taxa (e.g., humans, goats, sheep) (78, 97, 98), and in humans, the genetic variants of *EPAS1* that are enriched in Tibetan highlanders are associated with lower blood Hb concentration (98). However, it remains unclear whether blood Hb levels represent the direct phenotypic target of selection (5, 28). The HIF pathway is known to play a role in HPH and other responses to hypoxia as well (95, 96, 99), so it is possible that evolved changes in blood Hb concentration represent a secondary consequence of selection on another trait with an influence on O_2 transport.

Some evidence suggests that high-altitude natives have attenuated the activation or effects of the sympathetic nervous system in chronic hypoxia. The sympathetic nervous system is activated in acute hypoxia by the hypoxic chemoreflex, which increases systemic vascular resistance and

blood pressure, and causes α-adrenoreceptor–mediated vasoconstriction in many tissues to shunt blood flow toward core hypoxia-sensitive organs (i.e., brain and heart) (81, 100). Sympathetic activation and its effects decline partially but still tend to persist in chronic hypoxia, opposing the effects of local factors that promote vasodilation, such that vascular resistance and O_2 supply may be constrained to many tissues (100–102). However, hypoxic sympathetic activation appears to be blunted in Himalayan humans as compared to sea-level natives after high-altitude acclimatization (101). A similar reduction in hypoxic sympathetic activation may also exist in high-altitude deer mice, based on our observation that chronic hypoxia does not result in hypertrophy of their carotid body—the peripheral chemosensing organ that initiates the hypoxic chemoreflex—unlike what occurs in many low-altitude natives (32, 103). There is some inconsistency about whether effector tissues are less sensitive to sympathetic stimulation in high-altitude natives; heart rate is less sensitive to sympathetic agonists in both Tibetan plateau pika and Andean guinea pigs (104, 105), but femoral arteries from fetal and neonatal llamas have increased vasoconstrictor sensitivity to α-adrenergic stimulation as compared to lowland sheep (106, 107). Nevertheless, if sympathetic activation does occur in high-altitude natives, its effects on the vasculature could be offset by an upregulation of vasodilatory factors. Indeed, nitric oxide (NO) production appears to be elevated in Tibetan humans in association with enhanced systemic blood flow to peripheral tissues (108), and NO also contributes to significant baseline vasodilatory tone in fetal llamas (109). In general, although we are just beginning to understand the prevalence and mechanisms of evolved changes in sympathetic control in high-altitude natives, the current evidence suggests that the detrimental effects of hypoxic sympathetic activation may be reduced, along with the attenuation of other maladaptive responses to chronic hypoxia.

FUEL METABOLISM IN HIGH-ALTITUDE NATIVES

How might high-altitude natives balance the competing challenges of a constrained O_2 supply and the need to optimize nutrient use? The optimal substrate allocation in mammals involves energetic trade-offs that depend upon work rates and durations. Lipids are energy rich, support low work rates, and make up ∼80% of available energy stores in most mammals. Carbohydrate stores are relatively small (∼1% of total reserves) and generally support short-term bouts of high ATP turnover rates (45). However, the oxidation of glucose provides ∼16% greater ATP yield per mole of O_2 than the oxidation of fatty acids (110, 111). Thus, a greater reliance on carbohydrates represents a potential O_2-saving strategy that could be beneficial in high-altitude hypoxia (1). Consistent with this hypothesis, lowland men show an increase in carbohydrate use during exercise upon arrival, and after acclimatization to 4,300 m, when comparisons between sea-level control and hypoxic individuals were made at the same absolute work rate (112–115). However, current models of exercise fuel use in mammals (116) predict that relative work rate (i.e., exercise intensity relative to VO_2max) may primarily determine fuel use. The reduction in VO_2max experienced in hypobaric hypoxia results in a higher relative exercise intensity for a given absolute intensity (e.g., 65% versus 50% VO_2max at sea level), and correspondingly increases reliance on carbohydrates (43, 117). Studies where intensity is adjusted to reflect the depressive effects of hypoxia on VO_2max, such that individuals are compared at the same relative intensity, show that acclimatization leads to little change in how exercise is powered in lowland men and women (118–120). The same is true for laboratory rats (43, 121) and laboratory born and reared lowland native deer mice (26) after hypoxia acclimation. These data suggest that fuel use is not appreciably altered by hypoxia, despite the O_2-saving advantage of increasing carbohydrate use, possibly due to trade-offs associated with the risk of depleting this valuable and limited fuel store.

In contrast, current evidence suggests that highland mammals support cardiac and brain metabolism (122, 123) and submaximal exercise (22, 26) with a greater reliance on carbohydrates. In wild-caught Andean mice (genus *Phyllotis*) that were acclimated to sea-level conditions, two highland species had a higher reliance on carbohydrates to power aerobic exercise compared to two lowland species at the same relative intensity (22). A similarly augmented reliance on carbohydrates to fuel exercise was observed in highland deer mice that were born and bred in captivity at sea level, but only after acclimation to hypoxia (26).

Fuel use to support thermogenesis has not been extensively studied, but current evidence suggests that lowland humans and other mammals rely heavily on lipids for heat production during moderate rates of ST (124–126). Highland mammals appear to have an elevated capacity for lipid oxidation in hypoxia (21) that likely helps maintain elevated and sustained metabolic rates in the wild (15, 19). In fact, mass-specific rates of lipid oxidation in highland deer mice at cold-induced VO_2max are the highest ever observed in mammals, contributing to >80% of total heat production, and are threefold higher than the maximal rates during exercise in this species (26; N. Wall, C.E. Robertson, A.E. Schlater, L. Hayward, G.B. McClelland, unpublished observations).

Thus, mammals native to high altitude appear to overcome at least two main challenges in terms of substrate use supporting aerobic performance in hypoxia: (*a*) supporting higher rates of carbohydrate use than lowland mammals at the same relative exercise intensity and (*b*) maintaining very high rates of fatty acid oxidation for sustained thermoregulation. The underlying mechanisms responsible are currently not well understood, but the emerging evidence is discussed below.

Regulation of Exercise Glucose Oxidation at High Altitude

Flux control of circulatory glucose during exercise is distributed across several pathway steps, from glycogen stores to muscle mitochondria (127). Much like the O_2 transport cascade, highlanders may augment carbohydrate use by increasing the overall flux capacity of this pathway, which could involve changes in capacity at all steps in the pathway or modify the capacity and acute regulation of specific steps (**Figure 2**). Enhanced release of glucose from the liver could occur by increasing the capacity for glycogenolysis and gluconeogenesis, coupled with higher hepatic membrane conductance via the glucose transporters (GLUTs). Muscle uptake capacity could be enhanced by increasing the surface area of the capillary endothelium, increasing sarcolemmal density of GLUTs, or decreasing the overall diffusion distance for transport (40). However, the capacity to phosphorylate glucose by the hexokinase (HK) reaction has also been identified as an important bottleneck for muscle uptake during exercise (127, 128). Maximal rates of glucose oxidation are also partly determined by the capacity for glycolysis and pyruvate decarboxylation via active pyruvate dehydrogenase (PDH). It is not completely clear how all of these sites of regulation of carbohydrate flux have evolved in high-altitude natives, but our work suggests that deer mice of highland ancestry exhibit adaptive plasticity in the capacity for muscle glucose uptake by increasing HK activity in the gastrocnemius, and they also show higher mRNA for Glut1 and Glut4 compared to unacclimated mice (26). Highland deer mice also may have increased capacity for liver gluconeogenesis compared to lowland conspecifics, possibly as a way to enhance circulatory glucose availability (26).

Highlanders could augment carbohydrate use by modifying the acute regulation of steps in the carbohydrate transport pathway. Acute control of glucose flux with exercise is complex but has been extensively studied in humans and other lowland native mammals. The control of liver glucose release by insulin and glucagon is well characterized (127, 129). It is unclear how hepatic metabolism is regulated at high altitude, but resting blood levels of insulin and glucagon are similar in highland compared to lowland humans (130). High circulating levels of catecholamines during

exercise suggest that they too may have an important role in increasing glucose availability (127). For example, circulating epinephrine concentration, the rate of glucose appearance (Ra) into the circulation, and rate of disappearance (Rd) of glucose from the circulation can be positively correlated (113). High-altitude exposure modifies this regulation of glucose flux in lowland humans. Upon ascent to 4,300 m, both epinephrine and Ra and Rd glucose were elevated during the same absolute exercise intensity in lowland humans to support increased carbohydrate oxidation (113, 115, 131). It has been proposed that these events are causally related and that the corresponding increase in glucose use at high altitude is a consequence of stimulation of the sympathoadrenal system by the hypoxic chemoreflex (119). However, subsequent acclimatization partially (but not completely) reduces circulating epinephrine levels, but glucose turnover remains high in lowland men (131, 132), suggesting that epinephrine cannot entirely account for the changes in carbohydrate oxidation at high altitude. This possibility is also supported by the minimal influence of antagonists of α-adrenergic and β-adrenergic receptors on exercise glucose turnover rates (113, 127, 132, 133). However, differences in catecholamine levels could also result from differences in relative exercise intensity, and humans acclimatized to high altitude showed no difference in circulating catecholamines or carbohydrate use when compared to sea-level controls at the same percent VO_2max (118–120). Nevertheless, as described above, highland taxa may exhibit low sympathetic activity, but they still tend to oxidize carbohydrates at rates that are similar to or higher than those in lowland taxa during exercise, suggesting that differences in control by circulating catecholamines do not contribute to the evolved differences in exercise fuel use.

The metabolic phenotype of skeletal muscle should impact its capacity to oxidize glucose, and one might expect highland animals to have greater capacities for glycolytic flux and pyruvate oxidation. Indeed, O_2 consumption with pyruvate as a substrate was higher in permeabilized fibers of the gastrocnemius muscle in highland deer mice compared to lowlanders (76). However, data from highland mice show that carbohydrate oxidation rates are not necessarily correlated with the biochemical capacity of enzymes in glycolysis (21, 22, 25, 26, 33). For example, the apparent maximal activity (Vmax) of enzymes at key regulatory steps in glycolysis was no higher in highland Andean mice (22), nor was it higher in highland deer mice after hypoxia acclimation (with the exception of HK activity) (26), even though each exhibits elevated carbohydrate oxidation during submaximal exercise. These data suggest that regulation of glycolysis or of downstream steps by allosteric or covalent modulation contributes to differences in muscle glucose use in high-altitude natives. The enzyme PDH plays a particularly pivotal role in directing pyruvate toward oxidative phosphorylation. Covalent regulation by phosphorylation via PDH-specific kinases (PDKs) and dephosphorylation by phosphatases are important to determine pyruvate decarboxylation by PDH (134). PDH activity is greatly reduced in acute hypoxia, in part through the activation of PDK1 by HIF-1α (135). However, this is not a sustainable strategy at high altitude, because the low ATP yields and accumulation of lactate associated with anaerobic glycolysis would greatly limit scope for activity. In fact, highland humans show lower blood lactate accumulation during exercise in hypoxia compared to unacclimated lowlanders (136). This phenotype persists at sea level, which could suggest that there is an evolved (genetically based) change in the regulation of pyruvate metabolism in high-altitude natives. However, blood lactate accumulation during exercise is also reduced after hypoxia acclimation in lowland humans (136) and in laboratory mice (137). We have shown that this decline in exercise blood lactate is associated with a reduction in muscle HIF-1α and PDK1 expression and with an associated increase in PDH activity (137). Whether these or other mechanisms for regulating the metabolic fate of pyruvate have evolved in high-altitude natives is unclear, but a positive association between resting blood lactate and the highland variant of the HIF-2α gene *EPAS1* has been observed in Tibetan humans (138). However, as acknowledged

by Ge and colleagues (138), interpretations of metabolic flux and relative fuel use from static concentration measurements of plasma metabolites should be made with caution.

Regulation of Fatty Acid Oxidation During Thermogenesis at High Altitude

To support high rates of metabolic heat production, highland natives must maintain very high rates of fatty acid oxidation in hypoxia. At sea level, acute cold exposure activates the sympathetic nervous system, and the catecholamine-induced activation of hormone sensitive lipase mobilizes nonesterified fatty acids (NEFAs) from white adipose tissue (**Figure 2**) (139, 140). These liberated NEFAs are used by skeletal muscle and BAT to power heat production (139). A common response in lowlanders to acute or chronic hypoxia, even in warm conditions, is an increase in circulating NEFA (121, 141). This increase in NEFA availability was once thought to indicate an increased reliance on fatty acid oxidation for exercise (142) because plasma NEFA and circulatory turnover tend to correlate at sea level (143). However, even though more NEFA is available in the circulation, muscle fatty acid uptake rates decline in acclimatized lowlanders compared to those at sea level (termed the fatty acid paradox) (144). Furthermore, during aerobic exercise in lowland mammals at sea level, fatty acid oxidation reaches a plateau at modest intensities (116) and fails to increase when availability of circulatory NEFA is artificially elevated (e.g., 145). Given that fat oxidation rates in highland deer mice are threefold higher at cold-induced VO_2max than during aerobic exercise (26; N. Wall, C.E. Robertson, A.E. Schlater, L. Hayward, G.B. McClelland, unpublished observations), and that ST may account for up to 60% of this oxidation (17, 51), it is likely that highland mice somehow circumvent the limitations for muscle fat oxidation. Tibetan highlanders express genetic variants of peroxisome proliferator–activated receptor (*PPARA*) and show higher circulating NEFA at rest (138), but it is unclear if other highland animal taxa share this trait and if it leads to greater rates of lipid oxidation.

It is thought that muscle fiber uptake of circulating NEFA and the capacity for fat entry into mitochondria limit lipid oxidation rates (140, 146). Current evidence supports the fatty acid translocase (FAT/CD36) as an essential membrane transporter for the facilitated transport of NEFA into cells (140). Similarly, fat transport in the cytosol is mediated by fatty acid binding protein (FABP), and FAT/CD36 and FABP content in muscle both correlate with the proportional abundance of aerobic fibers (140). The gastrocnemius muscle of highland deer mice has a higher numerical density of type I fibers (25, 34), suggesting that there might be a correspondingly higher content of these important transport proteins. This muscle phenotype has been shown to correlate with higher rates of lipid oxidation in domestic house mice during exercise (147) and may indicate a greater capacity to use circulating NEFA. The capacity for entry into mitochondria involves the conversion of fatty acids into acyl-CoA, catalyzed by the enzyme acyl-CoA synthase (148). The enzyme carnitine palmitoyltransferase-1 plays a crucial role in controlling fatty acid oxidation by converting acyl-CoA to acyl-carnitines, and reductions in free carnitine during intense glycolytic activity may limit this process (140, 149). For example, as exercise intensity rises, higher rates of carbohydrate oxidation lead to excess production of acetyl-CoA. This is buffered by carnitine acetyltransferase to form acetyl-carnitine, reducing the inhibition of the PDH reaction, but depletes free carnitine levels available for acyl-carnitine formation. Therefore, to ensure high and sustained rates of fatty acid oxidation for shivering, highlanders must avoid a reduction in free carnitine either by maintaining higher baseline levels of free carnitine or by avoiding declines in this important intermediate by some other mechanism. Once in the mitochondrial matrix, the maximal rate of β-oxidation is set by enzyme activity, but little is known about the acute regulation of this pathway with increases in energy demand (140). Our previous work has shown that the gastrocnemius muscle of highland deer mice has a greater overall expression of genes involved in

NEFA: nonesterified fatty acid

Acyl-carnitine: formed in cells from acyl-CoA and carnitine by the enzyme carnitine palmitoyltransferase (CPT)-1

Acetyl-carnitine: formed in cells from acetyl-CoA and carnitine by the enzyme carnitine acetyltransferase

fat metabolism and greater capacity for β-oxidation (as reflected by activity of hydroxyacyl CoA dehydrogenase) than lowland *Peromyscus* (21, 26, 33). This appears to be a genetically fixed trait in highland mice that is resistant to hypoxia and cold acclimation (26; N. Wall, C.E. Robertson, A.E. Schlater, L. Hayward & G.B. McClelland, unpublished observations). This suggests that a higher capacity for fatty acid oxidation in the gastrocnemius muscle contributes to population differences in cold-induced VO_2max, but that it cannot account for increases in whole-animal lipid oxidation that occur with acclimation.

Circulating NEFA also supports NST by activating uncoupling protein (UCP)-1 and by serving as a substrate for the mitochondrial electron flux needed to support the heat production mechanism of BAT (**Figure 2**) (150). Recent evidence from laboratory mice reveals that BAT uses acyl-carnitines circulating in the plasma as a major fuel source and that these acyl-carnitines are produced in the liver from adipose tissue–derived NEFA (151). Highland deer mice have higher aerobic capacity and capacity for β-oxidation in the liver as compared to their lowland counterparts (26), which may allow for an enhanced production of acyl-carnitines to support NST. If so, carnitine may be an important metabolic intermediate for supporting high rates of both ST and NST at high altitude.

OXYGEN AND FUELS SHARE A CONVECTIVE TRANSPORT ROUTE IN THE CIRCULATION

Delivery of both O_2 and substrates to working tissues involves convective transport by the circulation. Many high-altitude natives have evolved higher cardiac outputs and/or capillarity in locomotory muscles, but has this arisen to enhance the transport of O_2, metabolic substrates, or both? One might predict that evolved changes in the circulatory system would be driven by the demands for O_2 transport in hypoxia, since O_2 cannot be stored to any great extent in most terrestrial mammals and birds. Selection for aerobic capacity in lowland mammals enhances circulatory transport capacity for O_2 more than for substrates (148, 152), but this question has not been directly examined in highland species. Metabolic substrates are primarily transported in the plasma, and hypoxia-induced increases in hematocrit can negatively influence the transport rates for substrates at equivalent cardiac outputs. Therefore, substrate supply to tissues may be appreciably greater in highlanders than in lowlanders, due to increased cardiac output at VO_2max and to the blunted increase in hematocrit in response to chronic hypoxia (3, 25), even in the absence of any changes in plasma substrate concentrations. The significantly higher capillary surface densities seen in the locomotory muscle of highland deer mice (25, 34) and other highland natives would also increase the conductance of substrates.

Water-insoluble NEFAs require albumin for circulatory transport, and the availability and binding capacity of this plasma protein can greatly influence rates of delivery. Interestingly, the albumin gene exhibits a remarkably high level of altitudinal differentiation in allele frequencies in deer mice (153). The mechanistic implications of this finding are unknown, but it is possible that low environmental temperatures are driving selection of enhanced circulatory transport capacity for NEFA. Interspecific differences in albumin's capacity to bind NEFA can exist, such as previous observations that dog albumin can bind 50% more NEFA than goat albumin in vitro, and these differences likely contribute to the greater circulatory transport and fat oxidation rates of some species during submaximal exercise (152). It is therefore foreseeable that albumin could have evolved in highlanders to support greater NEFA binding capacity. Alternatively, albumin also binds NO, and 80% of blood-borne NO exists as *S*-nitrosalbumin, so it is also possible that albumin has evolved in high-altitude natives to adjust the vasodilatory influence of NO in hypoxia (153).

OXYGEN AND FUELS CONVERGE AT MITOCHONDRIA

Aerobic performance relies upon adequate delivery of O_2 and metabolic substrates but also depends critically on the capacity of mitochondria in active tissues to support oxidative phosphorylation and fuel oxidation. It has long been appreciated that variation in aerobic performance is associated with variation in the mitochondrial quantity and quality of muscles and other active tissues. The volume density of mitochondria in locomotory muscles has often been associated with variation in VO_2max (56, 154, 155). There is also a growing appreciation that variation in the functional quality of mitochondria (e.g., respiratory control and/or capacity of a given volume of mitochondria) can contribute to variation in aerobic performance (156–158). In hypoxic environments, aspects of mitochondrial O_2 kinetics such as sensitivity of mitochondrial respiration to low O_2 may restrain rates of oxidative phosphorylation and fuel oxidation (159, 160). Aerobic performance at high altitude may depend critically on the capacities for oxidizing particular metabolic fuels, particularly in light of the above-described trade-offs in efficiencies of O_2 use between carbohydrate versus lipid fuels. How have these mitochondrial phenotypes evolved in high-altitude natives?

Whether and how mitochondrial respiratory capacity has evolved in high-altitude natives appear to depend on the species in question. The mitochondrial abundance of active tissues is elevated in species that have evolved to sustain long periods of intense metabolic activity at high altitude. For example, high-altitude deer mice have evolved a greater mitochondrial respiratory capacity in the gastrocnemius muscle (76), owing largely to increases in the proportional abundance of oxidative fiber types (25, 34) and to increases in mitochondrial volume density within these oxidative fibers (76). Similarly, bar-headed geese have evolved a greater abundance of oxidative fiber types in the flight muscle (75, 161). The more oxidative muscle phenotypes in these high-altitude natives could help augment thermogenic capacity and/or improve hypoxia resistance by increasing the total respiratory capacity of an entire muscle when intracellular O_2 tensions decrease and limit the maximum attainable respiration of a given volume of mitochondria (1, 162). However, not all high-altitude natives have evolved greater mitochondrial abundance and respiratory capacity. In fact, Tibetan and Sherpa humans have lower mitochondrial respiratory capacity and mitochondrial volume density in the vastus lateralis muscle, as compared to lowlanders at sea level or at high altitude (73, 163, 164). Human high-altitude natives have clearly evolved a number of adaptations that improve function at high altitudes (4), but they need not sustain the high metabolic rates of some other mammal and bird species at high altitude, which may explain these seemingly divergent evolutionary responses to high alpine life.

Mitochondrial respiration can become O_2 limited during intracellular hypoxia (159, 160), so it is possible that aerobic performance could be improved in high-altitude natives by evolved changes in mitochondrial O_2 kinetics that allow mitochondrial respiration to continue at lower O_2 tensions. This hypothesis has support from comparative studies in fish, in which there is a relationship between hypoxia tolerance and mitochondrial O_2 affinity (165). However, support for this hypothesis is equivocal in high-altitude natives. There are some modest changes in O_2 kinetics in high-altitude deer mice (reduced P_{50}, the PO_2 at which respiration is reduced by 50%, and/or greater catalytic efficiency for O_2 in some conditions) (76) but not in the high-altitude bar-headed goose (75). Therefore, evolved changes in mitochondrial O_2 kinetics may help improve aerobic performance in hypoxia in some but not all high-altitude taxa.

CONCLUSIONS

We have begun to define some of the mechanisms that allow highland native animal taxa to survive in hypoxic and cold high alpine regions. Thermogeneic capacity (cold-induced VO_2max) has been

shown to be under strong selective pressure in deer mice at high altitude (16). This phenotype involves both genetically fixed and phenotypically plastic subordinate traits. This includes not only morphological traits but also potential shifts in the regulation of pathway flux. This ensures adequate flux through the O_2 delivery pathway and the allocation of appropriate substrates that align with environmental optima. In many ways, we have only begun to scrape the surface in our understanding of how highland natives have evolved hypoxia resistance. Future work should aim to further uncover the underlying mechanisms that improve aerobic performance in hypoxia in highland natives.

FUTURE ISSUES

1. How has the capacity for phenotypic plasticity evolved in high-altitude natives, particularly in consideration of the multiple stressors at high altitude (hypoxia and/or cold) and the fact that plasticity may differ at different life stages (adult, perinatal, postnatal, or transgenerational)?
2. What are the relative roles of different steps in O_2 and substrate transport pathways for evolved changes in aerobic performance and hypoxia resistance?
3. What are the integrative mechanisms, from the regulation of protein activity up to the physiological system, for the evolution of the key determinants of O_2 and substrate transport and utilization in high-altitude natives?
4. What is the genomic architecture for the evolution of aerobic performance and hypoxia resistance in high-altitude natives?
5. What are the relative roles of different steps in the glucose and fatty acid oxidation pathways for evolved changes in fuel use for exercise and thermogenesis at high altitude?
6. How can variation in skeletal muscle phenotype help explain variation in fuel use for exercise and thermogenesis at high altitude? Can variation in the recruitment of different muscles help explain the observed changes in fuel use?

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General Interest

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