REVIEW-SYMPOSIUM

To what extent do physiological tolerances determine elevational range limits of mammals?

Jay F. Storz[1] and Graham R. Scott[2]

[1] *School of Biological Sciences, University of Nebraska, Lincoln, NE, USA*
[2] *Department of Biology, McMaster University, Hamilton, ON, Canada*

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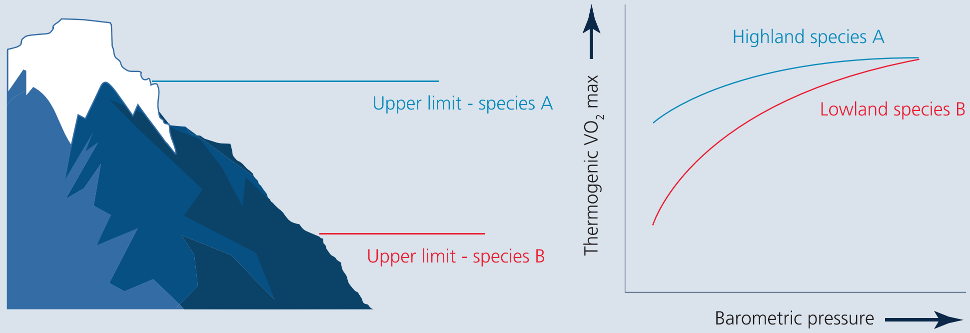

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Abstract A key question in biology concerns the extent to which distributional range limits of species are determined by intrinsic limits of physiological tolerance. Here, we use common-garden data for wild rodents to assess whether species with higher elevational range limits typically have higher thermogenic capacities in comparison to closely related lowland species. Among South American leaf-eared mice (genus *Phyllotis*), mean thermogenic performance is higher in species with higher elevational range limits, but there is little among-species variation in the magnitude of plasticity in this trait. In the North American rodent genus *Peromyscus*, highland deer mice (*Peromyscus maniculatus*) have greater thermogenic maximal oxygen uptake ($\dot{V}_{O_2\mathrm{max}}$) than lowland white-footed mice (*Peromyscus leucopus*) at a level of hypoxia that matches the upper elevational range limit of the former species. In highland deer mice, the enhanced thermogenic $\dot{V}_{O_2\mathrm{max}}$ in hypoxia is attributable to a combination of evolved and plastic changes in physiological pathways that govern the transport and utilization of O_2 and metabolic substrates. Experiments with *Peromyscus* mice also demonstrate that exposure to hypoxia during different stages of development elicits plastic changes in cardiorespiratory traits

Jay F. Storz is currently Willa Cather Professor of Biology at the University of Nebraska. Jay's research programme in integrative evolutionary biology investigates mechanisms of adaptation to high-altitude hypoxia in vertebrates, especially Andean mice. **Graham R. Scott** is currently an Associate Professor and Canada Research Chair at McMaster University. He is broadly interested in the physiological basis of how vertebrates respond and adapt to environmental challenges, and a major focus of his research are the cardiorespiratory and metabolic mechanisms of high-altitude adaptation in mammals and birds. Jay and Graham share a love of the mountains and the animals that live there. They have maintained a long-running collaboration on the physiology of high-altitude rodents in both North and South America.

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that improve thermogenic $\dot{V}_{O_2\max}$ via distinct physiological mechanisms. Evolved differences in thermogenic capacity provide clues about why some species are able to persist in higher-elevation habitats that lie slightly beyond the tolerable limits of other species. Such differences in environmental tolerance also suggest why some species might be more vulnerable to climate change than others.

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Correspondence author J. F. Storz: School of Biological Sciences, University of Nebraska, Lincoln, NE, 68588-0118, USA. Email: jstorz2@unl.edu

Abstract figure legend Hypothetical relationship between elevational range limits and capacity for aerobic thermogenesis (thermogenic maximal oxygen uptake) in hypoxia. In this hypothetical comparison between highland and lowland sister species, which is consistent with empirical data for small mammals, the species with the higher elevational range limit also has higher (mass-corrected) thermogenic capacity at low barometric pressures.

Introduction

> When we reach the Arctic regions, or snow-capped summits, or absolute deserts, the struggle for life is almost exclusively with the elements.
> Darwin (1859)

> …[F]or the global change biologist, the lack of physiological approaches is the primary barrier to the successful prediction of the ecological effects of climate change. A lack of mechanistic understanding of how organisms work makes it difficult to predict the potential threats to life on Earth.
> Bozinovic et al. (2011)

Understanding the causes of geographical range limits is a long-standing goal in biology (Kirkpatrick & Barton, 1997; Sexton et al., 2009). A corollary problem concerns the extent to which distributional limits of species are determined by intrinsic limits of physiological tolerance (Bozinovic & Naya, 2015; Bozinovic & Rosenmann, 1989; Bozinovic et al., 2011). Even in cases where ecological competition has an overriding influence on the ability of a species to persist at range margins, physiological tolerances might still play a decisive role because they can affect the outcome of competitive interactions. If a given species has compromised performance capacities in peripheral, range-edge habitats, it might be especially susceptible to being outcompeted and excluded from those habitats by other species that are able to maintain relatively higher performance capacities in the same environment.

Elevational shifts in species ranges are of special relevance in the context of global climate change, and the conservation implications of such shifts underscore the need to understand the physiological determinants of range limits and why some species might be more vulnerable to climate change than others (Somero, 2010). In mountainous regions, many bird and mammal species are expected to undergo upward elevational range shifts as they track changing temperature isoclines and associated shifts in vegetation, and such shifts have already been documented over surprisingly short time scales in several different parts of the world (Freeman & Freeman, 2014; Freeman et al., 2018; McCain et al., 2021; Moritz et al., 2008; Rowe et al., 2010, 2015; Tingley et al., 2012). If acclimatization to hypoxia enables lowland natives to colonize high-elevation environments successfully, highland natives might be 'pushed off the top' owing to competitive displacement. Alternatively, genetic adaptation of highland natives might confer a sufficiently durable home-field advantage that they can successfully outcompete lowland immigrants, which might then be 'squeezed in the middle'. In the highest alpine zones, a key question about elevational range shifts concerns the extent to which upslope habitat tracking of lowland natives might be impeded by physiological limits of hypoxia tolerance.

Hypotheses regarding physiological tolerance and range limits

Patterns of variation in species range limits across elevational and latitudinal gradients have suggested several hypotheses about the role of climatic variability in shaping geographical distributions. A well-supported empirical generalization, known as Rapoport's rule, is that the latitudinal midpoints of species distributional ranges are positively correlated with the latitudinal breadths of those ranges (Stevens, 1989). In other words, species with predominantly temperate-zone distributions tend to inhabit an especially broad range of latitudes, whereas tropical species tend to be more narrowly restricted. A physiological hypothesis to explain Rapoport's rule, known generally as the climatic variability hypothesis, posits that species that inhabit more polar latitudes must have the physiological capacity to tolerate an especially broad range of environmental conditions. The resultant expansion of niche breadth facilitates colonization of a diverse range of environments, hence species with broader tolerances tend to become more widely distributed. The same reasoning underlies Janzen's (1967) hypothesis that 'mountain passes are higher in the tropics', which suggests that tropical species with relatively narrow ranges of thermal tolerance might be less capable of colonizing high elevations in comparison to temperate-zone species that evolved to cope with seasonally variable climates.

The climatic variability hypothesis predicts a match between prevailing levels of climatic variability in the native range of a species and its breadth of environmental tolerance, attributable to evolved tolerance, increased acclimatization capacity (plasticity), or a combination of both. The hypothesis is agnostic regarding whether the increased breadth of tolerance is an evolved byproduct of adaptation to extreme or marginal environments or whether a pre-existing capacity for acclimatization is what enabled the species to colonize such environments in the first place (Bozinovic & Naya, 2015).

A positive correlation between range midpoint and range breadth is observed in some animal taxa that are distributed across elevational gradients (Stevens, 1992), but it is not a pervasive pattern in all vertebrate groups (McCain & Bracy Knight, 2013). Although high-elevation environments are uniformly colder and are generally characterized by increased climatic severity relative to lower elevations at a similar latitude, overall levels of climatic variability (as measured by the amplitude of daily or seasonal changes in temperature) are not necessarily higher. Thus, any parallels between species from more polar latitudes and higher elevations in terms of thermal tolerance and environmental niche breadth might have more to do with adaptation to climatic extremes rather than adaptation to climatic variability.

Physiological performance, thermoregulation and elevational range limits

Thermoregulatory capacities have often been invoked to explain upper latitudinal range limits in endotherms, especially in temperate-zone birds (Root, 1988; Swanson & Garland, 2009). In endothermic vertebrates that are distributed across elevational gradients, upper range limits can be determined by physiological responses to the combined stressors of both cold and hypoxia. In response to cold exposure, most eutherian mammals increase metabolic heat production in an effort to maintain body temperature. If the cold stress is sufficiently severe, it elicits the maximal rate of heat production. Most heat production is fuelled by aerobic metabolism and can therefore be quantified as the maximal rate of O_2 consumption ($\dot{V}_{O_2\max}$). This measure of thermogenic $\dot{V}_{O_2\max}$, also called 'summit metabolism', reflects the combined capacities for shivering thermogenesis (non-locomotory contraction of skeletal muscle that produces metabolic heat as a byproduct) and non-shivering thermogenesis (metabolic heat production that does not involve contraction and can occur in skeletal muscle, brown adipose tissue and other tissues).

At high elevation, the reduced availability of O_2 can limit capacities for aerobic thermogenesis (McClelland & Scott, 2019; Storz & Scott, 2019; Storz et al., 2010). For small, winter-active mammals that live at high elevation, the combination of increased thermoregulatory demand (owing to low temperature) and reduced capacity for aerobic thermogenesis (owing to low P_{O_2}) suggests how limits on thermogenic $\dot{V}_{O_2\max}$ could impose limits on maximal attainable elevations. In principle, an alpine species that is able to attain a higher thermogenic $\dot{V}_{O_2\max}$ than a lowland species could maintain a constant body temperature at lower ambient temperatures. The species with higher $\dot{V}_{O_2\max}$ would therefore be less likely to succumb to hypothermia and would be able to remain active in the cold for longer periods of time. Indeed, studies of free-ranging deer mice (*Peromyscus maniculatus*) have quantified the energetic challenges of life at high elevation (Conley & Porter, 1986; Hayes, 1989a, b) and have documented how natural variation in thermogenic $\dot{V}_{O_2\max}$ affects above-ground activity and survivorship during periods of extreme cold (Hayes & O'Connor, 1999; Sears et al., 2006, 2009). It is therefore easy to imagine how evolved differences in thermogenic capacity could enable some species to persist in higher-elevation habitats that lie slightly beyond the tolerable limits of other species.

In summary, thermogenic $\dot{V}_{O_2\max}$ in hypoxia represents a measure of integrated physiological capacity that is ecologically relevant for small endotherms living in high-elevation environments (McClelland & Scott, 2019; Scott & Dalziel, 2021; Storz & Scott, 2019; Storz et al., 2019). As a performance phenotype, it is well suited to the goal of connecting whole-animal physiology, environmental tolerance and elevational range limits. This is especially true for small endotherms, such as mice, that have high surface area-to-volume ratios and limited means of reducing thermal conductance and therefore experience especially high rates of heat loss that must be compensated by high rates of metabolic heat production.

Experimental evidence

Here, we use published data for wild rodents to evaluate the extent to which variation among species in elevational range limits might be explained by variation in thermogenic performance. We compare pairs of congeneric species with contrasting range limits from two groups of cricetid rodents: the South American genus *Phyllotis* and the North American genus *Peromyscus*. We summarize results of experiments to assess whether species with higher elevational range limits typically have higher thermogenic performance capacities in comparison to closely related lowland congeners. In all cases, the experiments used a 'common-garden' design, whereby animals were reared in uniform conditions to control for environmentally induced variation in performance. The term 'acclimatization' conventionally refers to a plastic physiological response to environmental stimuli in natural conditions, whereas the term 'acclimation' refers to a plastic response to experimentally produced stimuli in controlled laboratory conditions. We therefore use the term acclimation to refer to plastic changes in thermogenic performance elicited by experimental changes in temperature and/or P_{O_2}. In the comparison between species of *Peromyscus*, the tests were performed at levels of hypoxia that correspond to the upper range limits of the higher-dwelling species. We also use available data to assess evidence for species differences in plasticity in thermogenic performance and to gain insight into physiological mechanisms that underlie species differences.

Study taxa. In the case of South American *Phyllotis*, we make comparisons among a set of three species: *Phyllotis vaccarum*, a species with an extraordinarily broad elevational range (sea level to >6700 m; Steppan et al., 2022; Storz et al., 2020; Storz, Liphardt et al., 2023, b); *Phyllotis darwini*, a predominantly low-elevation species (sea level to ~2200 m; Steppan & Ramirez, 2015; Storz, Quiroga-Carmona et al., 2023); and *Phyllotis magister*, a predominantly mid-elevation species that is most abundant between ~2300 and 4000 m (Steppan & Ramirez, 2015) (Fig. 1*A*). *Phyllotis darwini* and *Ph. magister* are more closely related to one another than either is to *Ph. vaccarum* (Ojeda et al., 2021; Storz, Quiroga-Carmona et al., 2023). In the case of North American *Peromyscus*, we make comparisons between highland natives of the deer mouse (*Pe. maniculatus*), a broadly distributed species that inhabits elevations >4300 m, and the closely related white-footed mouse (*Peromyscus leucopus*), a predominantly lowland species that is not generally found at elevations >2000 m (Natarajan et al., 2015; Schweizer et al., 2019, 2021) (Fig. 1*B*).

In the case of both *Phyllotis* and *Peromyscus*, the species that inhabit the highest elevations also have the broadest elevational ranges. Moreover, the two highest-dwelling species in each genus (*Ph. vaccarum* and *Pe. maniculatus*) both have 'sky's the limit' distributions, because they occur on the summits of the highest peaks within their respective geographical ranges. In contrast, all other *Phyllotis* and *Peromyscus* species have elevational distributions with definable upper limits that are well below the highest summits.

Results for *Phyllotis*. Rezende et al. (2001) conducted common-garden measurements of cold-induced rates of O_2 consumption ($\dot{V}_{O_2}$) in normoxic conditions at 5°C in heliox. Heliox is often used for measurements of thermogenic performance owing to its greater thermal conductance than normal air. Heliox induces a more intense cold exposure, equivalent to temperatures ~20–30°C colder in normal air (depending on the species; Rosenmann & Morrison, 1974). Plasticity in $\dot{V}_{O_2}$ was measured as the change induced by a 30-day thermal acclimation to cold (5°C) *versus* warm (30°C) temperatures. Results revealed that the highest-dwelling species, *Ph. vaccarum* (referred to as *Phyllotis rupestris* by Rezende et al., 2001), had a higher cold-induced $\dot{V}_{O_2}$ than either of the two low-/mid-elevation species, *Ph. darwini* and *Ph. magister*. In fact, estimates of cold-induced $\dot{V}_{O_2}$ were concordant with the rank order of the elevations at

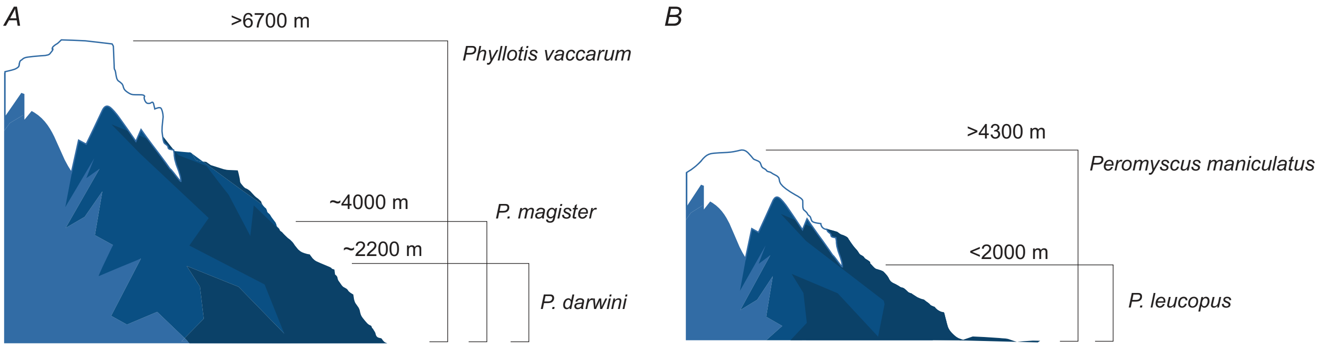

Figure 1. Schematic diagram of elevational distributions of select *Phyllotis* and *Peromyscus* mice
A, elevational ranges of *Phyllotis vaccarum*, *Phyllotis darwini* and *Phyllotis magister* on the western slope of the Andean Cordillera in South America. *B*, elevational ranges of *Peromyscus maniculatus* and *Peromyscus leucopus* in western North America.

which the study animals were captured (Rezende et al., 2001).

Although the study by Rezende et al. (2001) documented that the *Phyllotis* species with the highest elevational range exhibited a higher cold-induced $\dot{V}_{O_2}$ than the two low-/mid-elevation species, there was no detectable variation in the plasticity of this trait among species. Likewise, common-garden experiments that compared *Ph. darwini* from low- and mid-elevation thermal environments detected no population differences in plasticity for thermogenic performance (Bacigalupe et al., 2004). *Phyllotis* mice exhibit high levels of plasticity in metabolic traits in response to exposure to cold (Menéndez et al., 2022; Nespolo et al., 1999) and hypoxia (Schippers et al., 2012), but available data do not reveal any consistent patterns of variation in such plasticity among populations or species that are native to different thermal environments.

Results for *Peromyscus*. A series of experiments have compared thermogenic $\dot{V}_{O_2max}$ and its underlying determinants between highland deer mice and lowland white-footed mice. Mice of each species were bred in captivity, and adults were chronically exposed to hypoxia (12 kPa O_2) and/or cold (5°C) in a full factorial design (warm normoxia, warm hypoxia, cold normoxia and cold hypoxia). Tate et al. (2017, 2020) measured thermogenic $\dot{V}_{O_2max}$ in hypoxic heliox at −5°C. In these conditions, rates of heat loss exceed rates of heat production, such that body temperature tends to decline over the course of the 10–20 min trial. The $\dot{V}_{O_2}$ increases and reaches a stable plateau at thermogenic $\dot{V}_{O_2max}$, but $\dot{V}_{O_2}$ later falls as declines in body temperature intensify (with faster declines in mice having lower $\dot{V}_{O_2max}$). In small mammals such as deer mice, thermogenic $\dot{V}_{O_2max}$ typically equals or exceeds exercise-induced $\dot{V}_{O_2max}$ (Chappell & Hammond, 2004; Storz et al., 2019). Acclimation to cold hypoxia increased $\dot{V}_{O_2max}$ by 49% on average in highland deer mice and 42% in lowland white-footed mice, but $\dot{V}_{O_2max}$ was 15–20% greater in deer mice across treatments (Fig. 2*A*). This species difference in $\dot{V}_{O_2max}$ is reflected by differences in cardiorespiratory function, as revealed by instantaneous measurements on the experimental mice when they attained $\dot{V}_{O_2max}$. Acclimation to cold hypoxia increased cardiac output in both species (Fig. 2*D*), and it also increased total ventilation in deer mice (Fig. 2*B*). In white-footed mice, pulmonary O_2 extraction was relatively low in mice acclimated to warm normoxia, possibly owing to a relative hyperventilation at $\dot{V}_{O_2max}$, but pulmonary O_2 extraction increased after acclimation to cold hypoxia (Fig. 2*C*). The species differences in $\dot{V}_{O_2max}$ were associated with greater cardiac output

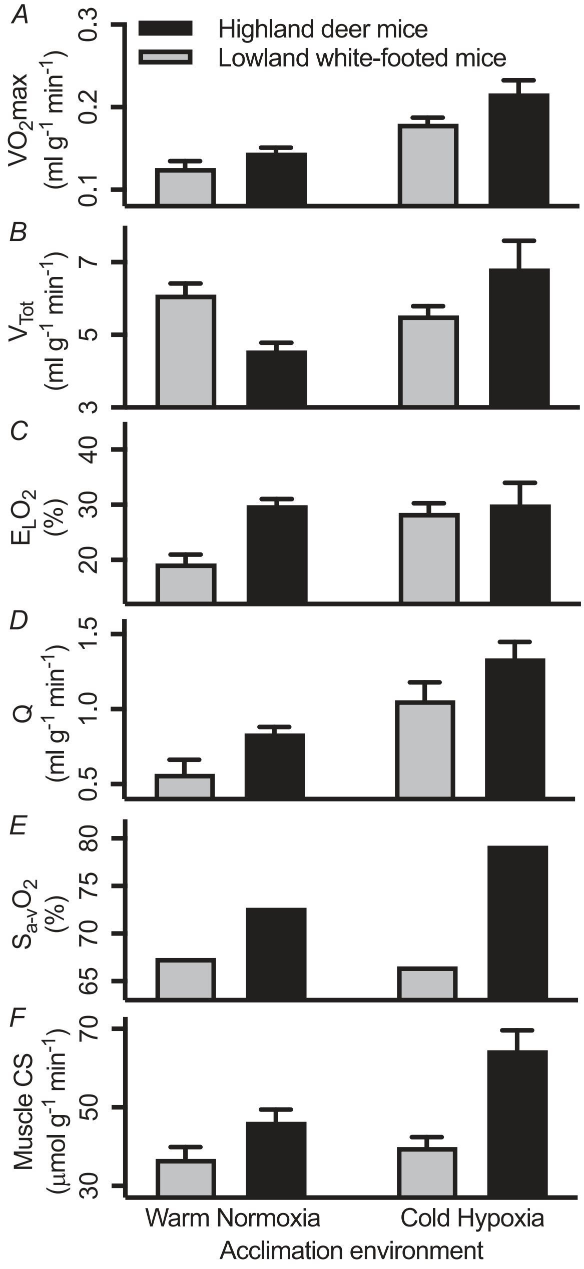

Figure 2. High-altitude deer mice have greater thermogenic $\dot{V}_{O_2max}$ in hypoxia than low-altitude white-footed mice, underpinned by differences across the O_2 transport pathway

There were significant species effects and/or species × environment interactions ($P < 0.05$) on: *A*, thermogenic $\dot{V}_{O_2max}$ (maximal O_2 consumption during acute exposure to severe cold); *B*, $\dot{V}_{tot}$ (total ventilation); *C*, E_LO_2 (pulmonary O_2 extraction); *D*, $\dot{Q}$ (cardiac output); *E*, S_{a-vO_2} (arteriovenous difference in O_2 saturation, for which only average values are available); and *F*, muscle CS (the activity of citrate synthase in the gastrocnemius, an important thermogenic muscle in the hindlimb). Data are means ± SEM, from Mahalingam et al. (2020) and Tate et al. (2020), where more details and exact *P*-values for the species and species × environment effects on each trait can be found.

and tissue O_2 extraction (as reflected by the arteriovenous difference in blood O_2 saturation) in deer mice compared with white-footed mice (Fig. 2*D* and *E*). White-footed mice have higher blood Hb content than deer mice, particularly after acclimation to cold hypoxia (Tate et al., 2020), but subsequent analyses suggested that the quantitative effects of this difference on $\dot{V}_{O_2}$ are more than offset by species differences in cardiac output and tissue O_2 extraction (Wearing & Scott, 2021; Wearing et al., 2021). Subsequent measurements in other studies also showed that the variation in thermogenic $\dot{V}_{O_2\text{max}}$ is mirrored by comparable variation in maximal oxidation rates of lipids, the primary metabolic fuel supporting thermogenesis (Lyons et al., 2021), and is associated with functional variation in thermogenic tissues. In highland deer mice, for example, skeletal muscle (gastrocnemius) exhibited greater citrate synthase activity (a marker of mitochondrial volume density; Fig. 2*F*) and highlanders responded to cold hypoxia with a more pronounced degree of mitochondrial uncoupling, which might augment non-shivering thermogenesis (Mahalingam et al., 2020). Cold hypoxia acclimation also increased non-shivering thermogenesis and the uncoupling protein 1 (UCP-1) content of brown adipose tissue in deer mice but not in white-footed mice (Coulson et al., 2021). These findings show that highland deer mice have greater thermogenic $\dot{V}_{O_2\text{max}}$ than lowland white-footed mice at a level of hypoxia that matches the upper elevational range limit of the former species. In highland deer mice, the augmented thermogenic $\dot{V}_{O_2\text{max}}$ in hypoxia is attributable to a combination of evolved and plastic (hypoxia-induced) changes in physiological pathways that govern the transport and utilization of O_2 and metabolic substrates.

Species differences in the influence of developmental hypoxia are also likely to contribute to differences in thermogenic $\dot{V}_{O_2\text{max}}$ and, hence, upper elevational range limits. The acclimation experiments discussed above revealed similar patterns of plasticity between species in response to cold hypoxia during adulthood, but individuals were raised in warm normoxia during perinatal and juvenile development, hence the effects of developmental plasticity were not explored in these studies. In lowland taxa, exposure to hypoxia in early development can result in neonatal mortality and fetal growth restriction (Moore et al., 2011; Wilsterman et al., 2023). In individuals that survive, exposure to hypoxia during early development can elicit different physiological adjustments from those elicited in response to exposure to hypoxia during adult life (Bavis, 2005; West et al., 2021). Perinatal hypoxia can lead to developmental programming that increases the risk of cardiovascular disease (e.g. hypertension) in adulthood (Galli et al., 2023; Giussani, 2021). Therefore, success at high altitude requires that species be able to survive perinatal hypoxia and avoid or overcome the developmental programming of hypoxia-induced disease. Success might also depend on plastic responses to developmental hypoxia that augment thermogenic $\dot{V}_{O_2\text{max}}$. Studies to explore this issue by Ivy et al. (2021) showed that lowland white-footed mice could not breed successfully in hypoxia (12 kPa O_2), because all pups were stillborn or died shortly after birth. Deer mice that are native to lowland environments can rear pups in hypoxia, but they suffer reduced birth weights (Wilsterman et al., 2023). In contrast, dams of high-altitude deer mice exhibit adaptive structural remodelling of the placenta that helps to maintain normal growth and birth weights in hypoxia (Wilsterman et al., 2023). Furthermore, continued exposure to hypoxia from conception into adulthood increased thermogenic $\dot{V}_{O_2\text{max}}$ by a far greater magnitude than acclimation to hypoxia during adulthood alone (Fig. 3*A*; Ivy et al., 2021). In mice that experienced developmental hypoxia, the enhancement of thermogenic $\dot{V}_{O_2\text{max}}$ was associated with increases in total ventilation (Fig. 3*B*), tidal volume and lung volume. These plastic changes in respiratory phenotypes are not induced by exposure to hypoxia during adulthood (Ivy et al., 2021). Subsequent measurements showed that developmental hypoxia also induced distinct patterns of gene expression in the diaphragm, the primary muscle driving inspiration, and that the differential expression of suites of co-regulated genes was correlated with differences in total ventilation and other respiratory traits (Schweizer et al., 2023). These findings show that highland deer mice can reproduce successfully in hypoxia and suffer no reduction in offspring growth. Hypoxia-induced plasticity during both pre- and postnatal development promotes a much larger increase in thermogenic $\dot{V}_{O_2\text{max}}$ than that produced by acclimation to hypoxia during adulthood alone, and the underlying physiological and regulatory mechanisms are distinct (Ivy et al., 2021; Schweizer et al., 2023).

Conclusions

In the case of *Phyllotis* and *Peromyscus*, the more broadly distributed, higher-dwelling species exhibited higher thermogenic performance relative to closely related species with lower range limits. This is consistent with results of comparative analyses of rodents, which revealed a negative correlation between mass-independent thermogenic capacity and the environmental temperature of the native habitats of the species (Bozinovic & Rosenmann, 1989; Rezende et al., 2004). In the phylogenetic comparative analysis by Rezende et al. (2004), minimum environmental temperature and native elevation were both statistically significant predictors of thermogenic $\dot{V}_{O_2\text{max}}$ in rodents. A negative correlation was also documented between environmental temperature and the capacity for non-shivering thermogenesis in rodents (Rodriguez-Serrano & Bozinovic, 2009). These patterns are consistent with predictions of the thermal niche expansion model, which proposes a causal connection between the evolution of high metabolic capacities and the ability to colonize new thermal environments (Block & Finnerty, 1994; Hayes & Garland, 1995; Swanson & Bozinovic, 2011).

We cannot yet draw general conclusions from comparisons involving only two genera of rodents, but if the positive association between thermogenic capacity in hypoxia and elevational range holds up with experimental results for additional species, it would suggest an important role for physiological tolerances in determining upper elevational range limits. One implication of such a finding is that an upward shift in elevational range of a given species might require adaptation to levels of hypoxia that are not encountered in the ancestral range. This would suggest that vulnerability to climate change is related to the evolvability of relevant physiological performance traits. If, in contrast, additional comparisons reveal that physiological performance in hypoxia is not always predictive of range limits, it would suggest that some groups of related species possess the latent capacity to acclimatize to levels of hypoxia that prevail at elevations beyond their present range limits. Such a finding would suggest that some lowland species are physiologically capable of colonizing higher elevations owing to an ancestral acclimatization capacity shared with highland relatives (phylogenetic inertia). The implication of such a finding would be that physiological tolerances *per se* are not the key determinants of range limits.

In a broader sample of species, experimental measures of thermogenic capacity in hypoxia hold the promise of providing mechanistic insights into the potential of species to evolve at range edges and might provide insights into the potential for range shifts in response to climate change, which is a key goal at the nexus of physiology, ecology, evolutionary biology and conservation.

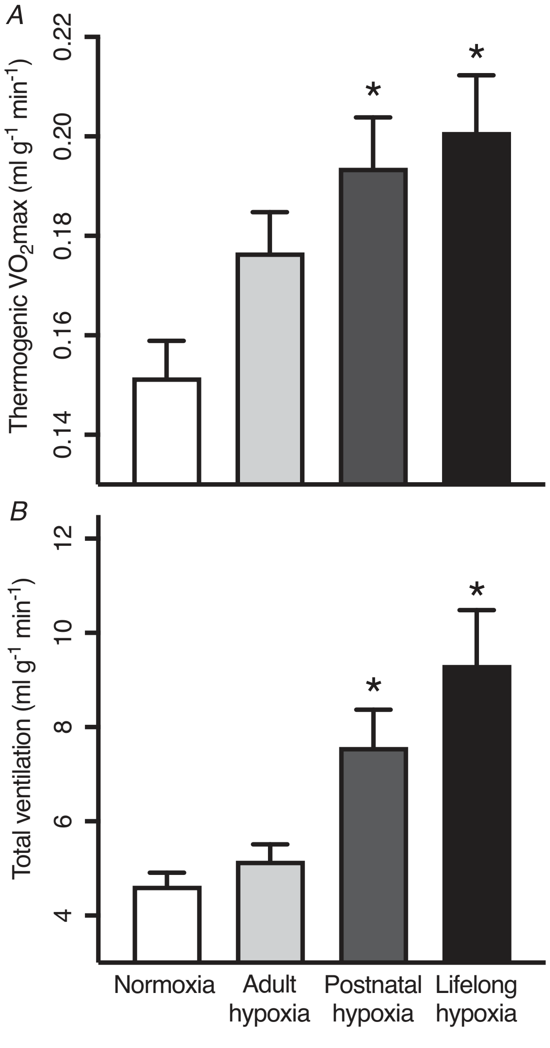

Figure 3. Developmental hypoxia increases thermogenic $\dot{V}_{O_2\max}$ and total ventilation in hypoxia in high-altitude deer mice

Treatment groups are as follows: normoxia controls; adult hypoxia, in which mice were acclimated to hypoxia (12 kPa O$_2$) for 6–8 weeks in adulthood; postnatal hypoxia, in which mice were exposed to hypoxia from birth to adulthood; and life-long hypoxia, in which parents were fully acclimated and allowed to breed in hypoxia, such that mice were exposed to hypoxia from conception to adulthood. *Significant pairwise difference from controls. Data are means ± SEM, from Ivy et al. (2021).

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Additional information

Competing interests

None.

Author contributions

J.S.: conception or design of the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work. G.S.: conception or design of the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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