

REVIEW

Developmental and reproductive physiology of small mammals at high altitude: challenges and evolutionary innovations

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ABSTRACT

High-altitude environments, characterized by low oxygen levels and low ambient temperatures, have been repeatedly colonized by small altricial mammals. These species inhabit mountainous regions year-round, enduring chronic cold and hypoxia. The adaptations that allow small mammals to thrive at altitude have been well studied in non-reproducing adults; however, our knowledge of adaptations specific to earlier life stages and reproductive females is extremely limited. In lowland natives, chronic hypoxia during gestation affects maternal physiology and placental function, ultimately limiting fetal growth. During post-natal development, hypoxia and cold further limit growth both directly by acting on neonatal physiology and indirectly via impacts on maternal milk production and care. Although lowland natives can survive brief sojourns to even extreme high altitude as adults, reproductive success in these environments is very low, and lowland young rarely survive to sexual maturity in chronic cold and hypoxia. Here, we review the limits to maternal and offspring physiology – both pre-natal and post-natal – that highland-adapted species have overcome, with a focus on recent studies on high-altitude populations of the North American deer mouse (*Peromyscus maniculatus*). We conclude that a combination of maternal and developmental adaptations were likely to have been critical steps in the evolutionary history of high-altitude native mammals.

KEY WORDS: Fetal growth, Gestational adaptations, High altitude, Maternal care, Post-natal development

Introduction: adaptation to high-altitude environments

‘One reason to focus on the physiology of juveniles and nestlings is that for most individuals it is the only physiology ever experienced’

Hill (1983).

The abiotic factors characteristic of high-altitude (HA) environments pose significant energetic challenges to their inhabitants. Animals endemic to alpine regions must cope with chronic cold exposure – as ambient temperature drops on average 2°C with every 300 m gain in elevation – alongside unremitting hypobaric hypoxia, which limits aerobic metabolism (Körner, 2007). This combination of stressors (hypoxia and cold) is particularly challenging for small endotherms whose high surface area to volume ratios promote rapid heat loss. The metabolic demands of this environment routinely push these small HA endotherms close to their $\dot{V}_{O_2, \text{max}}$ (see Glossary; Hayes, 1989). Yet, despite these energetic challenges, small rodents and lagomorphs are the animals with the highest altitudinal distributions across numerous mountain ranges (e.g. *Peromyscus maniculatus*, Hock, 1964; *Phyllotis*

xanthopygus, Kramer et al., 1999; *Ochotona curzoniae*, Ci et al., 2009). For example, the animal with the highest known distribution in the world is the yellow-rumped leaf-eared mouse (*P. xanthopygus*, adult body mass ~55 g), which was recently found to inhabit sites >6700 m above sea level (Storz et al., 2020).

Integrative studies of ecology, population genetics and physiology have identified numerous adaptations that allow small endotherms to thrive at HA despite significant and pervasive physiological challenges (reviewed in McClelland and Scott, 2019). With very few exceptions, studies on these small HA mammals have focused exclusively on the traits of non-reproducing adults (Ivy and Scott, 2015). In contrast to many HA-native bird species, small HA mammals inhabit mountainous regions year-round, meaning they undergo their entire reproductive cycle under conditions of chronic cold and hypoxia. Despite the fundamental importance of reproductive success for fitness, the reproduction, growth and development of these HA-adapted species has been largely ignored.

For young mammals, who are small and physiologically immature, the cold and hypoxic HA environment poses unique energetic and physiological challenges (both pre-natally and post-natally) compared with those experienced by adults. As such, developing mammals may require unique physiological solutions to cope with their environment. In addition, the physiology of developing mammals is inextricably linked to that of their mother, who shapes both the pre-natal and post-natal environment of her offspring (Wells, 2019; Wolf and Wade, 2009). The adaptive evolution of reproductive traits at altitude is therefore likely to be a function of both maternal and offspring physiology, as well as the complex interactions between the two (Fig. 1, arrows). In this Review, we discuss the energetic and physiological challenges posed by chronic hypoxia and cold to reproduction in small mammals, and we review what we know about the physiological adaptations during gestation and early life that have allowed some species to be highly successful at HA.

Pre-natal challenges

We have known for nearly a century that altitude directly challenges the very first steps in mammalian development. At altitude, fetal growth is reduced as much as 30% in lowland-native mammals, including mice, rats, guinea-pigs, humans and sheep (Bailey et al., 2019; Gilbert et al., 1979; Matheson et al., 2016; Parraguez et al., 2005, p. 200; Royer et al., 2000; Scheffen et al., 1990; Turan et al., 2017; Weihe, 1965). In addition, many lowland-native rodents experience increased rates of fetal death when gestating under experimental hypobaric hypoxia (Gilbert et al., 1979; Kelley and Pace, 1968; Matheson et al., 2016). Adaptation to altitude has ameliorated fetal growth restriction in the two mammals that have been studied to date: highland-adapted human populations (including native Andeans and Tibetans; Moore, 2017b) and multi-generational highland sheep (Parraguez et al., 2005). Although no one has yet examined the degree to which altitude adaptation may protect fetal growth in any small mammal, the dramatic effects of altitude on fetal

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Glossary**Implantation**

The process by which the blastocyst attaches to and, in some species, embeds itself within, the uterine wall. Implantation is the first step in placenta in which connections between maternal and fetal tissue are established. It is essential to the further development of the embryo and successful gestation.

Tidal volume

Volume of air taken into the lungs during a single breath.

Trophoblast

A class of cells that are derived from the outer layer of the blastocyst. Trophoblasts differentiate from a general stem cell type into an array of specialized trophoblasts that perform specific functions, including facilitating implantation and building the placenta.

 $\dot{V}_{O_2, \text{max}}$

Maximal whole-animal oxygen consumption, indicative of maximum capacity for aerobic metabolism. $\dot{V}_{O_2, \text{max}}$ can be elicited by exercise or cold. The exercise and cold-induced $\dot{V}_{O_2, \text{max}}$ values for a given individual are not always the same. Cold-induced $\dot{V}_{O_2, \text{max}}$ (thermogenic capacity, $\dot{V}_{O_2, \text{summit}}$) is the product of both shivering and non-shivering thermogenesis.

death rates and growth in lowland species suggest that fetal growth is a critical challenge that highland-resident small mammals must overcome.

In this part of the Review, we draw on literature exploring the effects of gestational hypoxia on the site of placenta in laboratory strains of lowland rodents, and literature focused on gestational hypoxia and altitude adaptation in humans and sheep. The physiological mechanisms underlying adaptive preservation of fetal growth at altitude in humans and sheep remain poorly resolved; however, there is substantial evidence from these species that multiple traits are likely to be important (Moore, 2017a). It should be noted that these models have some limitations related to their unique reproductive biology and evolutionary history that may restrict the extent to which patterns in their physiology are likely to be shared with small mammals at altitude (see Box 1 for further discussion).

The physiological traits relevant to fetal growth are both maternal and fetal. Essentially all major maternal physiological systems are modified by pregnancy to facilitate the metabolic demands of fetal growth (for a detailed review, see Napso et al., 2018). In particular, the respiratory, cardiovascular and hematological systems all increase their capacity or otherwise modify their function in order to facilitate sufficient gas exchange and nutrient delivery to the fetoplacental unit (Napso et al., 2018). Thus, the first major challenge to reproduction at altitude is ensuring that systemic changes to maternal physiology can fulfil delivery demands at altitude, where the partial pressure of oxygen is lower than at low altitude. Once oxygen (and nutrients) reach the site of implantation (see Glossary), their delivery and realized utility to the fetus depend on fetal hematolgy – which is particularly important for oxygen uptake – and of course on the structure and function of the placenta, which gates nutrient transfer between mother and fetus.

Maternal physiology

Chronic hypoxia at altitude may constrain fetal growth by inhibiting or altering gestational remodeling of maternal physiology, resulting in insufficient gas exchange and nutrient delivery to the implantation site. In humans, changes to maternal respiratory and cardiovascular function that occur in lowlanders at altitude are sufficient to match oxygen content in maternal circulation measured in highlanders (Moore et al., 2001; Zamudio et al., 2007b), suggesting that oxygen availability in maternal circulation is not the critical challenge for fetal growth at altitude (Postigo et al., 2009; Zamudio et al., 2007b; but see Julian et al., 2009). However, the physiological changes required to maintain blood oxygen content may confer costs that directly or indirectly limit fetal growth. For example, increases in hematocrit and hemoglobin content that occur in non-pregnant lowland humans and rodents at altitude persist during pregnancy (Gilbert et al., 1979; Julian et al., 2009; Nuzzo et al., 2018; Royer et al., 2000; Thompson et al., 2016; Zamudio et al., 2007b). Elevated hematocrit contributes to a general increase in blood viscosity in pregnant women (Kametas et al., 2004), which may increase flow resistance and thus impede local delivery or exchange of nutrients and gases at the implantation site and in the

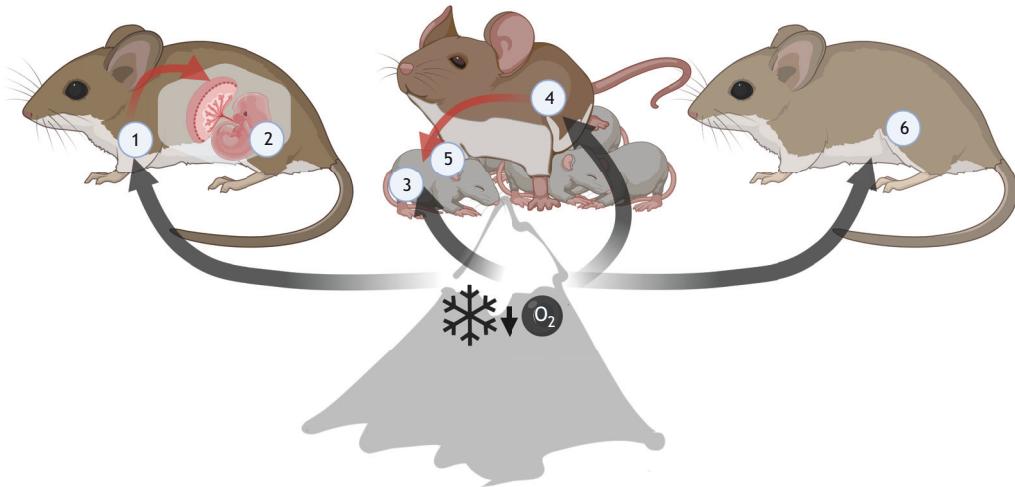


Fig. 1. The cold and hypoxic conditions of high-altitude environments act directly and indirectly on the physiology of small mammals at various life stages. Black arrows denote direct effects; red arrows denote indirect effects. (1) Maternal physiology during gestation; (2) nutrient transfer to the fetus via the placenta; (3) post-natal growth and development; (4) maternal physiology during lactation; (5) nutrient transfer to pups via nursing; (6) adult physiology. To date, only the direct effects of high-altitude adaptation on non-reproducing adults (6) have been well studied. Graphic designed using BioRender.

Box 1. Models for gestational adaptations to altitude

There is a long history of studying effects of hypoxia on fetal growth. However, the established model systems have limited value for identifying physiological mechanisms that preserve fetal growth in high altitude (HA)-adapted small mammals. Highland populations of humans and sheep have been the primary systems for studying HA adaptation and fetal growth. However, what we know about these systems may not apply to small mammals. The energetic challenges faced by large HA mammals are not equivalent to those of smaller species, whose higher mass-specific metabolic rates drive increased O₂ requirements and rates of heat loss, necessitating active thermogenesis. Additionally, the long generation time of humans and sheep relative to that of small mammals means that there has been less opportunity for evolutionary innovation in these groups (the influence of domestication in sheep notwithstanding). Both well-studied populations of HA-native humans (Andean, Tibetan) have resided at altitude for 11,000–25,000 years (Beall, 2007), which accounts for between 1000 and 2000 generations, and domestic sheep have resided at HA for no more than 500 generations (Parraguez et al., 2006). In contrast, HA deer mice native to the Colorado Rocky Mountains have been separated from their Great Plains conspecifics for ~200,000 generations (Natarajan et al., 2015). There has therefore been much more opportunity for selection to act on these smaller species with short generation times.

Research into hypoxia-dependent fetal growth restriction in small mammals has nearly exclusively utilized laboratory rodent strains, which are generally lowland-derived. These studies can thus only provide insight into lowlander challenges, not adaptative solutions. In addition, these studies primarily focus on the placenta, ignoring maternal acclimatization to the environmental stressor. This focus on the placenta is problematic because maternal gestational physiology, which is altered by altitude, determines the environment of the placenta and fetus, and thus provides critical context for changes to placental and fetal physiology. Finally, in the case of both laboratory rodents and sheep, many studies tend to use relatively short-term hypoxia exposure (e.g. only the final third of gestation). Short-term hypoxias, particularly nearer term, are problematic for understanding ecologically relevant responses to chronic hypoxia because they introduce the environmental stressor after the placenta has already completed critical developmental processes.

placenta. Indeed, elevated maternal hematocrit and/or hemoglobin levels have been linked to an increased risk of fetal growth restriction and other complications in humans at altitude (Gonzales et al., 2012, 2009; Khalid et al., 2016; Laflamme, 2011; Zamudio et al., 1993). Altitude-adapted deer mice and humans are able to preserve arterial oxygen saturation in circulation at altitude without similar increases to hematocrit thanks to adaptations spanning the oxygen-transport cascade (Beall, 2007; Bigham et al., 2013; Chappell and Snyder, 1984; Moore, 2017b; Scott et al., 2018; Storz et al., 2010; Tate et al., 2020), and thus they would not experience negative effects of increased blood viscosity and vascular resistance on placental function at altitude during pregnancy.

Vascular remodeling to increase the diameter or distensibility of blood vessels near the implantation site could moderate some of these changes to maternal hematology by altering local stress and strain and thus flow resistance. On the maternal side, the uterine artery is a critical site of vascular remodeling that is also well studied in the context of altitude adaptation. During healthy pregnancy at sea level, the uterine artery increases in diameter by more than three times to facilitate blood flows that will be 50–70 times greater at the end of pregnancy relative to the non-pregnant state (Boeldt and Bird, 2017; Mandala and Osol, 2012; Osol and Mandala, 2009). Uterine artery distensibility, or the ability for the vessel to expand in response to elevated intraluminal pressure, is also increased (Mandala and Osol, 2012; Mateev et al., 2006). When structural

and functional remodeling of the uterine artery and associated vasculature are insufficient, it increases the risk of vascular injury within maternal and placental blood vessels (Cartwright et al., 2010; Mateev et al., 2006) and directly affects the delivery of nutrients to the implantation site by limiting blood flow.

High altitude appears to inhibit both structural and functional remodeling of the uterine artery and associated vasculature at altitude. Women of lowlander ancestry gestating at altitude have smaller increases in uterine artery diameter across gestation than their sea level counterparts (Aksoy et al., 2015; Chen et al., 2002; Julian et al., 2008; Zamudio et al., 1995, 2007b, 2010) and, relative to those gestating at sea level, vascular resistance in the uterine artery of mothers at altitude is elevated in guinea-pigs (Turan et al., 2017) and humans (Aksoy et al., 2015; Chen et al., 2002; Julian et al., 2008; Zamudio et al., 1995, 2007b, 2010). Furthermore, the vasodilatory function of the uterine artery is deficient in lowland humans at altitude (Lorca et al., 2019), and the sensitivity of the smooth muscle cells of the uterine artery to changes in blood pressure is decreased in guinea-pigs under hypoxia (Mateev et al., 2006). In the case of guinea-pigs, we know that these changes contribute to increased mechanical strain within the vessel (Mateev et al., 2006). Failure of the uterine artery to sufficiently remodel to support blood flow during pregnancy may be related to hypoxia-dependent inhibition of cell replication: DNA synthesis in the uterine artery of pregnant guinea-pigs is lower under chronic hypoxia (Rockwell et al., 2000).

Highland adaptation appears to have modified the sensitivity of uterine artery remodeling to chronic hypobaric hypoxia. Highland-adapted humans are able to achieve larger uterine artery diameters and lower resistance indices at altitude (Charles et al., 2014; Dávila et al., 2010; Julian et al., 2009; Moore et al., 2001; Zamudio et al., 2007b). The relevant mechanism(s) are unknown, but in humans an allele for the gene *PRKAA1* has been linked to larger gestational uterine artery diameter and is under positive selection in Andean women (Bigham et al., 2014). For small mammals, gestational remodeling of the uterine artery diameter and vasodilatory function (and thus blood flow) in each uterine horn is a function of local (i.e. fetoplacental) processes (Fuller et al., 2009; Whitney et al., 1993), meaning that litter size and the density of implantation sites along each uterine horn may contribute to the degree to which the uterine arteries are able to achieve sufficient remodeling under chronic hypoxia.

Fetal physiology

Fetal hematology is also altered by gestational hypoxia. For example, fetal hematocrit and hemoglobin content increase at altitude in both humans and guinea-pigs (Gilbert et al., 1979; Postigo et al., 2009). However, adaptation to altitude does not blunt this effect in human fetuses (Postigo et al., 2009), and there is no evidence for adaptations to fetal hemoglobin structure in HA natives (Storz, 2016). Despite this, in humans, Andean fetuses still display an increased hemoglobin–oxygen binding affinity at altitude relative to ancestrally lowland fetuses at altitude, suggesting that there are still some unidentified adaptations in fetal physiology (Postigo et al., 2009). This could be important for the maintenance of fetal–maternal O₂ gradients, as many HA-adapted species have evolved higher-affinity adult hemoglobin, which could impede O₂ unloading at the placenta (Storz, 2016).

Placenta structure and function

The placenta plays an important role in determining the effects of altitude on fetal outcomes, both because it is the major mediator of nutrient transport between maternal and fetal circulations and

because its structural and functional development are highly sensitive to hypoxia. The placentas of rodents and lagomorphs contain two distinct compartments: a vascular compartment, where nutrient exchange occurs, and an endocrine compartment, which plays a critical role in connecting maternal and fetal vasculature and in organizing maternal physiology. Both these compartments are modified by gestational hypoxia, although the impact of these changes on fetal growth is not as clear. In rats and mice, the implantation site and placenta tend to display increased vascularity under gestational hypoxia (Soares et al., 2017), facilitating greater blood flow and nutrient delivery and exchange. However, increased blood flow may come at a cost of increased endoplasmic reticulum stress within the placenta (Matheson et al., 2016; Yung et al., 2012). Increased oxidative damage in the placenta at HA has only been reported in laboured placentas, where the ischemia/hypoxia caused by the process of labour may drive differences in these markers (Kurlak et al., 2016; Nuzzo et al., 2018; Parraguez et al., 2011; Tissot van Patot et al., 2010; Zhou et al., 2013). Placentas from high-altitude pregnancies at mid-gestation or following cesarean sections at term do not appear to experience increased oxidative damage (Matheson et al., 2016; Zamudio et al., 2007a).

At altitude, the vascular compartment of the placenta is also characterized by a reduction in the diameter of fetal capillaries, which may increase the surface area to volume ratio of the surface across which gas and nutrient exchange occurs (Burton et al., 1996; Espinoza et al., 2001; Khalid et al., 2016; Parraguez et al., 2010; Scheffen et al., 1990; Tissot van Patot et al., 2003, 2004). HA-adapted humans display similar decreases in the diameter of fetal capillaries at altitude (Jackson et al., 1987a,b), suggesting that the increase in the surface area to volume ratio may indeed be adaptive.

The endocrine compartment of the placenta, termed the junctional zone in rodents, tends to undergo hypertrophy under gestational hypoxia (Soares et al., 2017). Behavior of the invasive trophoblast (see Glossary), a sub-type of trophoblast arising from the junctional zone that is responsible for invading and remodeling maternal vasculature, is also critically affected by gestational hypoxia in species including rats and guinea-pigs. Hypoxia increases the depth of invasive migration into maternal tissues by these cells (Soares et al., 2017), potentially allowing for more extensive vascular remodeling. However, chronic hypoxia also appears to inhibit the remodeling behavior of these cells (Soares et al., 2017; Zhou et al., 2013). Insufficient remodeling by trophoblasts is likely to be harmful for the fetus because it leads to insufficient blood flow and/or elevated blood pressure, which can collapse the structures across which nutrient and gas exchange occur; thus, we might expect to find that highland adaptations to altitude should preserve or even expand invasion and remodeling at the site of implantation. However, in a mouse knock-out for PRL7B1, a signaling molecule that is critical for trophoblast invasion, the mice that lacked invasive trophoblasts displayed improved pregnancy success under hypoxia relative to wild-type animals (Bu et al., 2016). A major caveat to these findings is that mice do not have extensive trophoblast invasion under normoxia or hypoxia, and thus it provides limited insight into the adaptive role of trophoblast invasion for species with more extensive invasion, including humans, rats and guinea-pigs. To date, no data exist on HA native mice or other species where trophoblast invasion and remodeling are more modest, which could speak to this fundamental question about the extent to which trophoblast invasion contributes to fetal growth outcomes at altitude.

Altitude-dependent structural changes to the lowlander placenta and surrounding vasculature described above are occurring

alongside functional changes (such as changes to gene expression) that further affect nutrient transport to the fetus. In particular, glucose utilization by the feto-placental unit appears to be altered by altitude, such that the placenta relies more heavily upon glucose and delivers less to the fetus (Royer et al., 2000; Sakuragawa et al., 1988; Tissot van Patot et al., 2010; Vaughan et al., 2019; Zamudio et al., 2010, 2006). In addition to nutrient transporters, the placenta produces a large number of hormones that remodel maternal physiology across gestation. These hormones are primarily synthesized by cells derived from the junctional zone (Soares et al., 2017). Placental prolactins are the major family of placental hormones responsible for gestational remodeling of maternal physiology (Napsø et al., 2018), and they are critical for facilitating trophoblast–vascular interactions and remodeling vascular structure in and around the placenta (Soares et al., 2017). Broader changes to the transcriptional landscape of the placenta are thought, in part, to reflect shifts in the differentiation pathways taken by trophoblasts (i.e. the number or proportion of cells adopting specific trophoblast sub-types) (Bu et al., 2016; Soares et al., 2017, 2006); thus, additional consideration of the effects of hypoxia on trophoblast cell behavior and function are warranted.

Preparing for the post-natal period

Maternal physiology during gestation is not simply about facilitating fetal growth *in utero*. Fat accretion, remodeling of neural circuitry and maturation of the mammary glands towards the end of gestation set the stage for successful lactation and parental care (Napsø et al., 2018). Placenta-derived hormones that influence these late-gestation processes may therefore also be important components of successful reproduction at altitude, particularly in altricial species; however, the effects of altitude on late-gestational placenta function as it relates to post-natal maternal success have not yet been explored in any system to our knowledge.

Post-natal challenges

Once young HA mammals are born, they must contend with chronic cold and hypoxia, both of which limit post-natal growth and survival in low-altitude (LA) natives (e.g. Farahani et al., 2008; Hill, 1972; Weihe, 1965).

The maturity of HA neonates at birth is likely to be an important factor influencing the adaptive evolution of post-natal development. The mammalian inhabitants of the most extreme altitudes are primarily altricial, meaning that they are born relatively immature with little to no thermoregulatory capacity (Pembrey, 1895). For all altricial rodents, regardless of altitude, the post-natal period is precarious. Mortality rates during the first weeks of post-natal development in the wild can range from 49% to 96% (e.g. Bendell, 1959; Howard, 1949). These high mortality rates coincide with the time when many major physiological systems (e.g. thermoregulation, respiratory control) are developing and are sensitive to the environment. As a result, although certain traits that are thought to be important adaptations to HA (e.g. high-affinity hemoglobin; Ivy et al., 2020) may be present at birth in these altricial species, many of these traits do not develop or become functional until much later in these species (e.g. Adams et al., 1999; Agbulut et al., 2003; Barnard et al., 1970; Chew and Spencer, 1967; Dubowitz, 1963; Dzial et al., 2020; Gokhin et al., 2008; Goldspink and Ward, 1979; Hill, 1976; Lagerspetz, 1966). Given the low likelihood of survival during the post-natal period, anything that can confer a fitness benefit will probably be under strong selection at HA (Hill, 1983).

Below we have outlined developmental adaptations in three physiological systems in the well-studied HA-native populations of

the North American deer mouse. Notably, all these systems are also under selection in adults of this species, and we describe the adult traits for comparison. These adult adaptations are reviewed extensively in Storz et al. (2019). The post-natal adaptations were discovered using a common garden experimental design, where wild-caught HA and LA mice, native to the same latitude but different altitudes (300 m versus >4300 m above sea level), were bred in captivity for two generations. Pups were compared with the closely related but strictly LA white-footed mouse (*P. leucopus*). These experiments allowed us to isolate the effects of the environment and ancestry (genotype) on the ontogeny of a physiological trait (Fig. 2A). It is important to note that these studies focus on a single subspecies of HA deer mouse native to the Colorado Rocky Mountains (*P. maniculatus nebrascensis*), where gene flow between LA and HA elevations is limited. This population has been separated from the conspecific LA controls used in these studies for ~200,000 generations (Natarajan et al., 2015). Mitochondrial gene sequence homologies suggest that various HA subspecies of deer mice, native to different mountain ranges, tend to be more closely related to each other compared with their geographical closest LA counterparts (Natarajan et al., 2015). However, it is unclear whether the developmental adaptations discussed below are common to other HA subspecies, particularly *P. maniculatus sonoriensis*, native to the California White Mountains, where gene flow between elevations is much more prevalent (Natarajan et al., 2015; Snyder et al., 1982). Geographical variation in HA sites is an important factor to consider in future studies.

Brown adipose tissue function

Adult HA-adapted mice (*P. maniculatus*) have a higher thermogenic capacity (cold-induced $\dot{V}_{O_2, \text{max}}$) than their LA conspecifics (Cheviron et al., 2012, 2013; Hayes, 1989). This whole-animal trait, which is a function of both shivering and non-shivering thermogenesis (NST), is under positive selection at HA (Hayes and O'Conner, 1999), and it improves survival and increases activity levels in the cold (Sears et al., 2006). In deer mice and other small rodents, a major component (>50%) of whole-animal thermoregulatory capacity is brown adipose tissue (BAT)-based NST (McClelland et al., 2017; Van Sant and Hammond, 2008). BAT is unique to placental mammals though marsupials may contain BAT-like structures (reviewed in Jastroch et al., 2018). BAT is characterized by lipid-rich brown adipocyte cells with a high mitochondrial density. These mitochondria express uncoupling protein-1 (UCP-1), which dissipates the proton gradient established by the electron transport chain across the inner mitochondrial membrane. This uncouples the production of ATP from the oxidation of fuel, creating a futile cycle that generates heat. UCP-1 is activated when BAT is sympathetically recruited in response to cold (Cannon and Nedergaard, 2004). BAT activity is higher in wild adult HA deer mice compared with wild-caught LA *Peromyscus* (Velotta et al., 2016). BAT is present, although non-functional, at birth in most altricial species and develops faster than skeletal muscle (Barnard et al., 1970). As a result of this rapid maturation, early thermogenesis in these animals is driven exclusively by BAT-based NST, whereas shivering thermogenesis matures later.

Surprisingly, in HA deer mouse pups, BAT does not become functional until significantly later in development compared with lowlanders (Robertson et al., 2019). Unlike lowland *Peromyscus*, who begin to actively thermoregulate at 8 days old (Hill, 1983; Robertson et al., 2019), neonatal HA mice cannot use BAT to maintain body temperature during early post-natal development. This delay in BAT activation appears to be due to reduced sympathetic

regulation of the tissue and a coordinated suppression of metabolism (Robertson et al., 2019; Velotta et al., 2020). In many species of LA rodents, post-natal exposure to hypoxia or cold alters the rate of BAT maturation: cold tends to accelerate BAT maturation whereas hypoxia suppresses it (Denjean et al., 1999; Morrison et al., 2000; Mortola and Naso, 1997, 1998; Skála and Hahn, 1974). However, BAT function does not appear to be sensitive to rearing environment in highlanders (Velotta et al., 2016). The developmental delay in BAT function is coordinated by a suite of regulatory genes that are under directional selection at HA (Velotta et al., 2020), suggesting that suppressing BAT function during development is a functional adaptation to the HA environment. This is an example of physiological heterochrony, an evolved change in the developmental timing of a physiological trait (Gould, 1977; Spicer, 2006). We discuss the potential adaptive benefits of such a delay below.

Skeletal muscle phenotype and function

In endotherms, skeletal muscle performs the dual function of locomotion and thermogenesis via shivering. Many HA-adapted mammals and birds have evolved a more oxidative and/or highly vascularized adult muscle phenotype (Hepple et al., 1998; Kayser et al., 1991; León-Velarde et al., 1993; Lui et al., 2015; Mahalingam et al., 2017; Mathieu-Costello et al., 1998; Scott et al., 2009; Sheafor, 2003). In adults, this probably confers both a higher running $\dot{V}_{O_2, \text{max}}$ and a greater capacity and endurance for shivering. Muscle metabolism is also altered in HA species, with HA adults having a greater capacity for both lipid and carbohydrate oxidation (Lau et al., 2017; Lui et al., 2015; McClelland et al., 2017; Schippers, et al., 2012).

In deer mice, whole-animal $\dot{V}_{O_2, \text{max}}$ (running and cold induced) is sensitive to HA rearing environment (Chappell et al., 2007; Russel et al., 2008). However, the specialized HA muscle phenotype itself is genetically fixed (Nikel et al., 2018; Scott et al., 2015). As stated above, skeletal muscle is immature at birth in altricial species. For example, in both newborn LA and HA deer mice, muscle fibers are small and poorly vascularized, and muscle metabolic phenotype is not yet established (Robertson and McClelland, 2019).

In HA deer mice, the characteristic aerobic muscle phenotype of adult mice does not appear until several weeks after birth. Up until this point, the skeletal muscles grow at the same rate as those of LA pups (Robertson and McClelland, 2019). However, prior to the phenotype divergence, many genes associated with muscle metabolic processes are down-regulated in HA pups (Velotta et al., 2020), and – unlike LA pups – young HA mice are unable to shiver. Overall, despite cold-induced $\dot{V}_{O_2, \text{max}}$ being elevated in HA adults, neonatal HA pups have a much lower thermogenic capacity relative to lowlanders, due to delays in both shivering and non-shivering thermogenesis throughout post-natal development (Fig. 2B). Suppression of thermogenesis lasts from birth until weaning at 3 weeks of age (Robertson et al., 2019). See below for further discussion.

Breathing pattern and O₂ sensing

A primary challenge that LA natives encounter when they ascend to greater altitude is that of efficiently transporting enough oxygen to their mitochondria for oxidative phosphorylation. One way in which HA-adapted mammals and birds have overcome this hurdle is by altering respiratory physiology (reviewed in Ivy and Scott, 2015). For example, HA deer mice and HA plateau pikas (*O. curzoniae*) have evolved a deeper tidal volume (see Glossary) compared with their LA counterparts (Ivy and Scott, 2017; Pichon et al., 2009). This altered breathing pattern allows them to take up oxygen more efficiently compared with lowlanders.

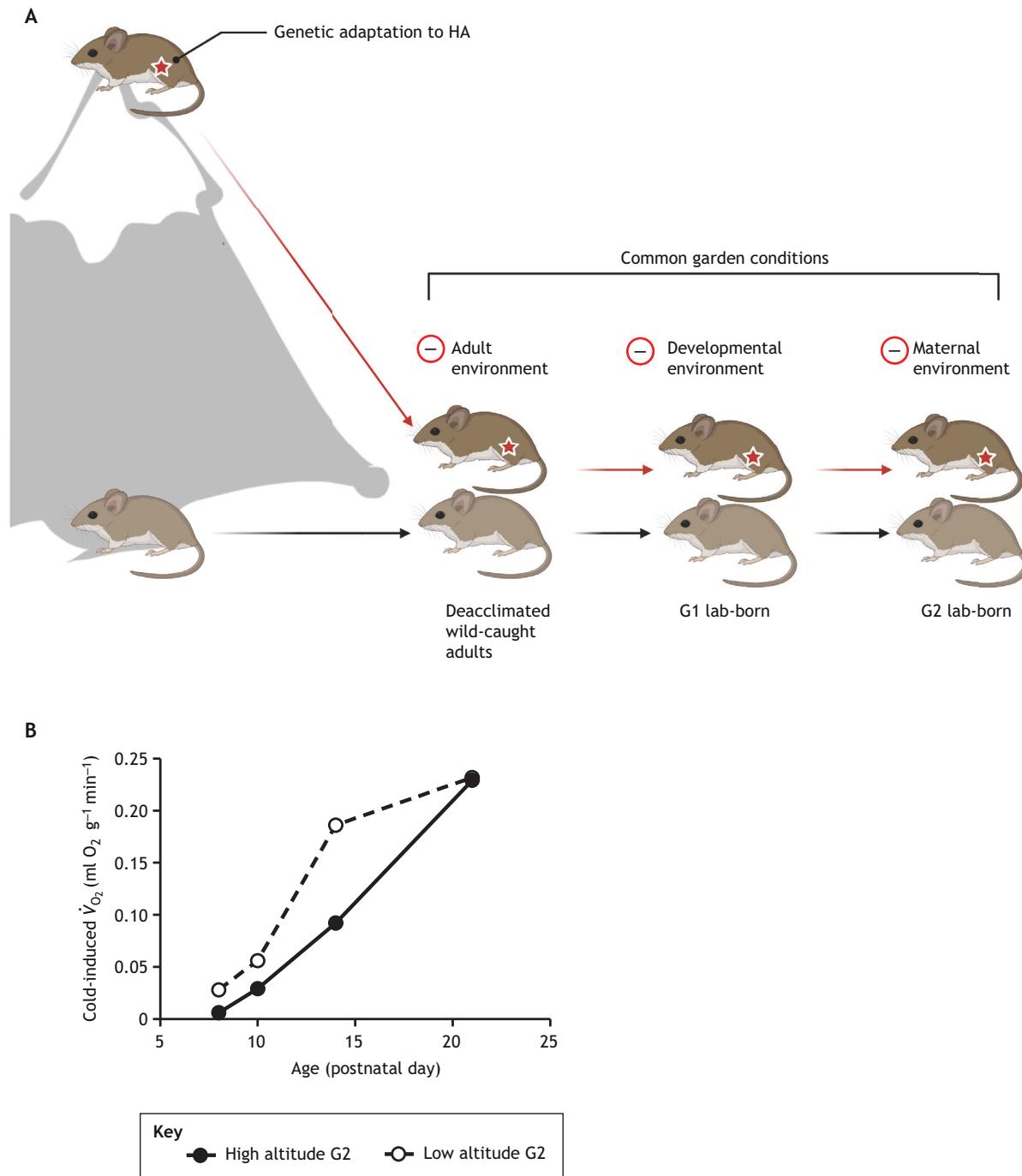


Fig. 2. Testing for physiological adaptations to high altitude during development. (A) A multi-generation (G), common garden experimental design allows us to isolate the effects of ancestral, developmental and maternal environment on a given physiological trait. In the wild, an individual's phenotype is driven by a complex interaction between genotype and environment, as well as persistent effects of their rearing environment (pre- and post-natal) and carry-over effects of the environment on their mother. Each generation under common garden conditions removes one of these effects until theoretically only genotypic influences on phenotype remain. (B) Using this design, we see that a slower maturation of thermoregulatory mechanisms has evolved in high altitude (HA)-adapted *Peromyscus maniculatus*. The metabolic responses (cold-induced $\dot{V}O_2$) to acute cold exposure (10 min at 24°C, post-natal days 8 and 10; 10 min at -5°C, post-natal days 14 and 21) are reduced throughout post-natal development until weaning (post-natal day 21) in G2 HA-adapted *P. maniculatus* (Robertson et al., 2019; Robertson and McClelland, 2019; Velotta et al., 2020). These pups are raised under common conditions, so this response is driven primarily by underlying genetic adaptations (Velotta et al., 2020). We hypothesize that suppressing metabolically costly thermogenesis has evolved at HA, to allow pups to conserve energy for growth. Experimental design figure made in BioRender.

During early post-natal development, the breathing pattern of young mammals is insensitive to hypoxia. The chemosensory cells of the carotid bodies, which normally sense arterial O_2 saturation and trigger

an increase in ventilation when oxygen levels drop (hypoxic ventilatory response), are insensitive to hypoxia at birth in all mammals studied to date (Carroll and Kim, 2013). In HA deer mice, it takes longer for the

carotid bodies to mature, and the ventilatory sensitivity to hypoxia is delayed relative to that of lowlanders (Ivy et al., 2020). Additionally, the more effective altered breathing pattern that is characteristic of adult highlanders is not established until several weeks after birth (Ivy et al., 2020). Interestingly, the delay in the establishment of a mature breathing pattern and sensitivity to hypoxia matches the developmental delay in the onset of endothermy in HA deer mice.

Why delay developmental function of adaptive phenotypes at HA?

The studies described above show that, at least in one species, delaying the maturation of critical physiological systems during the nursing period is likely to be adaptive in HA environments. These findings are counterintuitive, particularly because these delays occur in the systems directly responsible for responding to low oxygen and temperature. What are the possible fitness benefits that make these delays adaptive?

Young altricial neonates are not as sensitive to perturbations in homeostasis as adults. For example, 4-day-old *Peromyscus* pups can survive several hours at a body temperature close to freezing without suffering any adverse consequences (Hill, 2017). If cold neonates are passively rewarmed by an external heat source (i.e. their mother), they do not incur the metabolic cost that would normally be associated with re-warming (Currie et al., 2015; Geiser et al., 2002). At least one other small, altricial mammalian species, the desert hamster (*Phodopus roborovskii*) has been shown to use a 'precocial torpor' strategy early in post-natal development to save energy in the cold (Geiser et al., 2019). Additionally, most small mammals tend to be far less sensitive to low oxygen as neonates than as adults (reviewed in Dzial et al., 2020). It is therefore possible that it is adaptive for HA neonates to conserve limited energy for growth rather than using energy to mount costly physiological responses to low oxygen and ambient temperature. Under cold alone, the benefits of thermoregulation outweigh the metabolic cost: lowland altricial mammals tend to accelerate the maturation of thermoregulatory systems when reared in the cold (Barnard et al., 1970; Morrison et al., 2000), and some cold-adapted species – for example, the Norwegian lemming – have evolved the ability to thermoregulate earlier after birth than most other altricial rodents studied (e.g. mice, rats or golden hamsters; Lagerspetz, 1966). However, hypoxia also affects the timing of the development of both thermoregulation (Mortola and Naso, 1997, 1998) and the hypoxic ventilatory response (Bavis, 2005). We can therefore only speculate that the combination of cold and hypoxia at HA makes the suppression of lowlander responses the most cost-effective strategy.

Maternal care from birth to weaning

During the early post-natal period, HA mammalian mothers with altricial young must act as both a source of heat and as a source of food (Hill, 1972). This creates a significant energetic burden for animals that already operate close to their $\dot{V}_{O_2, \text{max}}$ (Hayes, 1989). In mice, milk output during lactation accounts for ~50% of the energy derived from food (Johnson et al., 2001). In fact, lactation is widely considered to be the most energetically costly life stage for a female mammal (Speakman and McQueenie, 1996). Successfully provisioning offspring under extreme conditions was likely to have been one of the critical evolutionary challenges faced by HA-adapted species.

Short breeding seasons at HA relative to LA sites of the same latitude limit the number of litters that a HA female can birth each year. To compensate, it is likely that HA mothers must invest heavily in the few litters that they have (McLean et al., 2019; Smith and McGinnis, 1968). Small HA mammals tend to give birth to larger litters than their LA conspecifics (e.g. *P. xanthopygus*, Sassi

et al., 2018; *P. maniculatus*, Dunmire, 1960; Halfpenny, 1980; Robertson et al., 2019). For those species that do not have large litter sizes – for example, HA North American pikas (*Ochotona princeps*, average of one to two pups) – mothers still completely deplete their fat reserves during lactation, suggesting that they are maximizing their reproductive investment (Miller, 1973).

Hypoxia tends to limit milk production in lowland mammals (e.g. Bruder et al., 2008; Moore and Price, 1948; Walton and Uruski, 1946; Weihe, 1965). Decreases in milk output under hypoxia can be partially alleviated by supplementing nursing mothers with a high fat diet, which increases milk fat content (Weihe, 1965). LA-native wild house mice (*Mus musculus*) raised for 10 generations in the cold (3°C) produce high fat content milk, which improves offspring growth and body composition (Barnett and Dickson, 1984). It is possible that small HA mammals also increase the fat content of their milk, although this has not been seen in the few large HA mammals studied to date (humans, yaks and dairy cows: Barsila et al., 2014; Bartl et al., 2009; Qiao et al., 2013; Quinn et al., 2016). Therefore, the mechanism by which HA mothers produce enough milk to provision their offspring is unclear. Regardless, the energetic cost of lactation at HA is likely to be quite high.

One way to support the metabolic costs of lactation at HA is a complementary increase in food intake. At LA, mammalian mothers remodel their digestive tracts to increase nutrient absorption during gestation and lactation. Cold exposure has a similar effect on food intake, increasing nutrient assimilation by increasing the size of digestive organs. The combination of lactation and cold stress act synergistically to further increase food intake in rodent mothers (Hammond et al., 1994; Hammond and Kristan, 2000). In fact, it has been suggested that food intake during lactation is limited by a mother's ability to dissipate metabolically produced heat (the heat dissipation limit hypothesis; for a review, see Speakman and Król, 2010). Therefore, in cold environments, lactating females consume more food than would otherwise be possible (Johnson and Speakman, 2001). However, hypoxia is a known anorexic agent, and it decreases food intake in lactating rats (Bruder et al., 2008). In non-lactating adult *P. maniculatus* the increase in food intake seen in the cold is partially ablated at 3800 m above sea level (Hammond et al., 2001). Rigorous ecological studies of HA females are required to determine whether food intake during lactation increases in the wild.

HA mothers also invest in their offspring through various forms of maternal care. Many measures of maternal behavior (e.g. time spent nursing, incubating and grooming pups, nest-building) vary considerably amongst individual rodents in the laboratory and in the wild (Champagne et al., 2003). For example, wild mice spend more time nursing when population density is low and thus competition for food is reduced (Stewart and McAdam, 2014). Importantly, in lowland altricial species, when mothers spend more time foraging, pup growth suffers from the combination of less milk and increased thermoregulatory costs to the pups (Hill, 1972). Rodents also alter their nest size or complexity in response to low temperatures, and those native to cold climates tend to build larger, more complex nests (King et al., 1964; Phifer-Rixey et al., 2018). Variation in maternal care (e.g. grooming) can have long-lasting epigenetic consequences for offspring phenotype, programming metabolism, the stress response and their own care behavior (reviewed in Champagne, 2008). Although maternal behavior is sensitive to environmental conditions, there is also a genetic basis to many of these traits (Bendesky et al., 2017). As such, altered maternal care phenotypes can evolve in different environments. To our knowledge, adaptation of maternal behavior to HA has not been studied, and this would be an interesting area for future research.

Conclusions

The combined cold and hypoxic conditions of HA present significant metabolic challenges to young mammals that specifically limit growth. Maternal physiology is also directly influenced by cold and hypoxia. As a result, in HA environments, resource transfer from mother to offspring may be limited during both pregnancy and lactation, compounding the direct effects of cold and hypoxia on young mammals. Previous research has shown that these environmental effects make it almost impossible for lowlanders at HA to successfully reproduce and grow. We propose that for a species to successfully establish at HA, both maternal and developmental phenotypes must evolve together. The fact that very little is known about the adaptive strategies used by these animals means there are many exciting avenues for future study.

Along with the direct impact of cold and hypoxia on each life stage, which we have outlined above, animals living at HA also deal with the cumulative effects of prior exposure to HA conditions that can affect fitness throughout their lifetime. For example, a pregnant female who is unable to properly remodel her mammary glands, neural circuitry and fat accretion during gestation due to hypoxia will be unprepared to provide sufficient nutrients and care to her pups during lactation. Insufficient maternal remodeling during pregnancy could thus exacerbate the effect of cold and hypoxia on nursing and other care behaviors, further limiting energy transfer to pups that must grow under cold and hypoxia. Females from such litters who survive to adulthood will be likely to display long-lasting effects on body condition that will limit their own future reproductive success. Thus, what happens during a single reproductive attempt will affect the future chances of success for both mother and offspring.

Finally, moving forward, it is important to remember that young altricial mammals are not simply small adults. They do not have the same physiological tools available to cope with environmental stressors. As such, any given physiological system (e.g. thermoregulation) may need to respond very differently to the same selective pressure across life stages. By focusing exclusively on adult physiology, we may miss many of the physiological innovations that are critical for adaptation in resident species. Studies of HA reproduction and development provide an important framework for comparative physiology, as the two main selective pressures (cold and hypoxia) are well understood. However, the same kinds of energetic limitations to growth and reproduction probably appear across all extreme environments.

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Competing interests

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