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Effects of Developmental Hypoxia on the Vertebrate Cardiovascular System

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Developmental hypoxia has profound and persistent effects on the vertebrate cardiovascular system, but the nature, magnitude, and long-term outcome of the hypoxic consequences are species specific. Here we aim to identify common and novel cardiovascular responses among vertebrates that encounter developmental hypoxia, and we discuss the possible medical and ecological implications.

embryo; fetus; heart; hypoxia; programming

Introduction

An organism is most sensitive to its environment during early development. Even minor changes in temperature, oxygen, or pH can lead to adaptive responses that can alter embryonic and fetal morphology and physiology (1). If the environmental stress occurs during critical developmental periods, the phenotypic changes are often permanent and persist into adulthood (2). Epigenetic changes in gene expression may also be triggered, which means that the environment during development can program traits that are heritable (3, 4). Furthermore, adverse conditions during development may influence the reproductive capacity of offspring (5). Therefore, environmental fluctuations during early life can have profound and persistent effects on organismal structure, function, and behavior across generations.

Insufficient oxygen supply (hypoxia) is one of the most pervasive and disruptive environmental stressors during embryonic and fetal development (6–9). For mammals, oxygen levels within the womb are tightly regulated to normal values at ~25 mmHg. This level of oxygen is considerably lower than arterial values in adulthood (~100 mmHg), but it is sufficient for fetal tissue requirements and it promotes healthy fetal and placental development (10, 11). However, human fetal arterial P_{O_2} (Pa_{O_2}) can sometimes be halved to 12 mmHg [equivalent to the mother breathing 10% oxygen saturation ($\%O_2$)] during pregnancy complications, such as in placental insufficiency, preeclampsia, gestational diabetes, and even maternal obesity, which lead to detrimental outcomes (12). In contrast to mammals, many birds and oviparous ectothermic vertebrates (fish, amphibians, and reptiles) develop with little or no parental care and are often exposed to wide fluctuations in oxygen. For example, embryonic birds can experience hypoxia at 12–16%O_2 (13) due to nesting behaviors in mounds, burrows, or alpine regions (13–20), and embryonic reptiles can be exposed to oxygen tensions ranging between 10%O_2 and 21%O_2 (21, 22). But possibly the most severe levels of hypoxia are found in the habitats of embryonic and larval fish, where some species develop in lakes and ponds with $<$1%O_2 (23). At the extreme, these environments may become completely devoid of oxygen (anoxia) (24). Thus, there is no "normal" oxygen concentration for most embryonic birds and ectothermic vertebrates. Given these constraints, natural selection is likely to have favored the evolution of traits that protect avian and ectotherm embryos from hypoxia.

The vertebrate cardiovascular system is particularly sensitive to developmental hypoxia, as it is the first line of defense against oxygen deprivation. In mammals, the lack of oxygen causes fetal cardiovascular adjustments that permanently remodel the heart and program disease susceptibility in adulthood (12, 25, 26). Embryonic birds share many of the cardiovascular responses to developmental hypoxia with fetal mammals (8, 27), but far less is known about ectothermic vertebrates. Importantly, there are major differences in metabolism and cardiovascular physiology between vertebrates. First, the metabolic rate of embryonic ectothermic vertebrates is much lower than that of endotherms, and, similar to that of bird embryos, it will vary according to the temperature of the environment. Whereas developmental temperature in mammals is set at a narrow range of 37–39°C, it can vary from 31°C to 39°C in birds (13), from 27°C to 38°C in reptiles (13), and from subzero to 43°C in fish (28, 29). Second, cardiovascular design varies dramatically among the vertebrate classes; fish have a single circulation with a two-chambered heart, most reptiles and amphibians have a dual circulation with a three-chambered undivided heart, and all crocodilians, birds, and mammals have a dual circulation with a completely divided four-chambered heart (30). It is likely that all of these factors will play a role in dictating the vertebrate response to hypoxia.

Given the widespread occurrence of developmental hypoxia across diverse habitats and vertebrate

species, a comparative analysis of vertebrate responses to developmental hypoxia will contribute knowledge toward a broad range of issues. From a clinical and physiological perspective, comparing the responses between viviparous and oviparous animals allows us to separate the direct effects of developmental hypoxia without the additional influences from the maternal and/or placental physiology (reviewed in Ref. 8). From a physiological and ecological perspective, comparing the limits of vertebrate developmental plasticity may help to predict species dynamics due to climate change. Therefore, the aim of this review is to provide a platform for a comparative discussion of the phenotypic consequences of developmental hypoxia on the vertebrate cardiovascular system. We do not discuss the numerous and diverse responses to developmental hypoxia in each vertebrate species, as this is beyond the scope of this focused review. Rather, we aim to identify common and novel cardiovascular phenotypic signatures among vertebrates as a consequence of developmental hypoxia and discuss possible implications.

Embryonic and Fetal Cardiovascular Responses to Hypoxia in Vertebrates

Embryonic and fetal vertebrates have three main options to acclimate to hypoxia: increase oxygen extraction, decrease oxygen consumption, and/or increase the efficiency of oxygen utilization (12). The overall response is unique to each species and highly dependent on the timing, severity, nature, and duration of the hypoxic insult, which mediates broad changes in cardiovascular structure and function (25). Nevertheless, some common signatures have emerged.

Modulation of Heart Rate

Most embryonic and fetal vertebrates respond to acute hypoxia (minutes) with a reduction in heart rate (32). This response is thought to lower the metabolic demand of the heart, leading to reduced myocardial oxygen consumption (12). However, it should be noted that Fisher et al. (33) found no change in fetal cardiac oxygen consumption after 15 min of acute hypoxia (descending aortic P_{O_2} at 14 mmHg), despite a 20% reduction in heart rate. Whether fetal cardiac oxygen consumption decreases immediately after the onset of acute hypoxia, when the fetal heart rate is at its nadir, or during greater levels of fetal hypoxia has not yet been investigated. The hypoxic bradycardia also serves to increase myocardial contractility and maintain cardiac output through the Frank–Starling mechanism, by prolonging end-diastolic filling time and thereby end-diastolic volume (34). In birds, reptiles, and fish, the bradycardia may not be evident in early incubation or with mild levels of acute hypoxia, but a reduction in heart rate is consistently observed in the latter 70% of incubation (35–39). However, in situations where developmental hypoxia becomes chronic (days to months), the initial bradycardia recovers in mammals and birds, and heart rate remains at control levels (40–43). In contrast, American alligators exposed to $\leq$10%O_2 at 10–90% development maintain bradycardia throughout (44–46), and the same conditions either cause no change (6, 44, 47) or significant tachycardia (48–50) in snapping turtles and scincid lizard heart rate. Tachycardia is also the common response in embryonic and larval zebrafish exposed to mild levels of chronic hypoxia, but this develops into a bradycardia when the level of hypoxia is more severe ($<$5%O_2) (51–53). Thus, in contrast to endothermic vertebrates, modulation of heart rate in ectothermic vertebrates appears to be an important mechanism to control cardiac output during extended periods of developmental hypoxia.

Vascularization and Oxygen Carrying Capacity

Under normal conditions, oxygen extraction in most embryonic and fetal vertebrates is extremely efficient because of the expression of functionally distinct high-affinity hemoglobin isoforms (54). Nevertheless, reductions in oxygen saturation of the arterial blood can trigger adaptations that improve oxygen carrying capacity and delivery. For example, hypoxia leads to an increased expression of embryonic hemoglobin in fish (55) and a stimulation of hematopoiesis in most birds (56), fish (57), reptiles (58, 59), and mammals (60, 61). Hypoxia is also a major stimulator of angiogenesis in the chorioallantoic membrane of fish (62), reptiles (63), and birds (56), which serves to improve oxygen extraction at the site of gas exchange. Similarly, in mammals, early-onset gestational hypoxia remodels the placenta (64), increasing placental volume and the fetal capillary surface area (65).

The Brain-Sparing Effect and Asymmetric Growth Restriction

The well-established "brain-sparing" circulatory response is another common phenotypic signature in fetal mammals, designed to support vital tissues at the expense of less important organs (32). In this response, acute hypoxia triggers differential vasomotion, consisting of constriction in the vasculature of peripheral organs, such as the hindlimbs, and vasodilatation in hypoxia-sensitive organs, such as the brain. Consequently, the fetal cardiac output is redistributed to maintain perfusion of the developing central nervous system with adequate levels of oxygen and other nutrients (32, 34, 66). Although protective in the short term, sustained fetal brain sparing can result in asymmetric growth restriction where fetal mammals including primates conserve head size at the expense of body

length or they are thin for their length (67). The redistribution of blood flow favoring the brain has also been demonstrated in the chicken embryo in the second half of incubation (68), and there is an apparent increase in brain blood flow in hypoxic snapping turtles from 70% of incubation (69). Numerous studies have shown that chronic hypoxia also causes growth restriction in embryonic fish, reptiles, and birds (6, 39–41, 44–46, 58, 70–85). Importantly, whereas chronic hypoxia reduces embryonic body mass and body length in American alligators, snapping turtles, Florida red-bellied turtles, and leopard geckos, the total incubation time is unchanged (6, 40, 44–46, 58, 70, 76, 77, 82, 86). Similarly, some models of chronic hypoxic pregnancy in rats do not reduce gestational length (87), but lambs from hypoxic pregnancies tend to be born a few days earlier (88).

Similar to mammals, birds, and reptiles, hypoxia leads to slower tissue growth rates (51, 89–92) and growth retardation (57, 89, 93–99) in fish. However, fish may represent an outlier with respect to the embryonic/fetal brain-sparing effect. To our knowledge, there is no evidence of asymmetric growth restriction in fish, and recent in vivo imaging of zebrafish larvae chronically exposed to hypoxia [8%O_2 from 1 to 15 days postfertilization (dpf)] has shown that brain blood flow is unchanged (57), despite a redistribution of blood flow. Instead, it appears that blood flow is driven from the zebrafish gut to the so-called red layer of muscle, which has been implicated in the uptake of oxygen in early larvae (100). Therefore, oxygen extraction may be the priority in hypoxic zebrafish larvae. Nevertheless, it is also possible that the reflex cardiovascular responses required for the brain-sparing effect may only exist in the latter stages of zebrafish development, after 15 dpf. Interestingly, in contrast to the human or sheep, fetal animals of highland species, such as the llama, show no increase in brain blood flow during acute hypoxia (101), with no increase in oxygen extraction across the brain (102). Instead, there is a fall in fetal brain O_2 consumption and temperature, together with a decrease in the activity of Na^+-K^+-ATPase and in Na^+ channel expression, which serves to reduce metabolic demand and protect against seizures and neuronal death (103).

Cardiac Enlargement or Sparing

In addition to asymmetric growth restriction, the sustained vasoconstriction and redistribution of blood flow associated with embryonic/fetal brain sparing can cause systemic hypertension (60, 104). The resulting increase in cardiac afterload can trigger cardiac enlargement, which is sometimes observed in fetal rats and sheep (105, 106). More commonly, mammalian fetal heart mass is unchanged during chronic hypoxia ("spared") and body weight is reduced, leading to an increase in the heart-to-body weight ratio (25, 61, 105–109). This latter phenotype is also the dominant response in chronically hypoxic embryos from chickens, American alligators, snapping turtles, and Florida red-bellied turtles (37, 45, 58, 71, 86, 110). However, cardiac hypertrophy has been reported in the lizard gecko and the snapping turtle late in development (45, 77), and some studies have even found thinning of the ventricular wall in chickens (72, 111, 112). In embryonic zebrafish, chronic hypoxia initially causes a reduction in heart size, but cardiac hypertrophy occurs once they reach the larval stages (62, 113–115). It is not clear why these studies have such discrepancies between species and vertebrate classes, and there seems to be no clear correlation between the response and experimental variables such as species, stage of development, and/or the severity of the hypoxic exposure. Interestingly, Crossley's group identified specific stages of development in which reptiles were particularly sensitive to hypoxia (e.g., critical windows) and showed that cardiac enlargement in alligators and turtles precedes, and is distinct from, the critical window for somatic growth restriction. This suggests that, at least in reptiles, embryonic cardiac hypertrophy is a targeted and direct response to hypoxia, rather than an indirect outcome of reduced somatic growth (43, 46).

Adrenergic Sensitivity

Sensitization of the sympathoadrenal medullary system is another hallmark of the vertebrate response to developmental hypoxia. First, basal levels of plasma norepinephrine and/or epinephrine are increased in hypoxic fetal sheep (116–119), fetal llamas (102), embryonic chickens (120–122), and embryonic alligators (41). The density, expression, and sensitivity of β-adrenergic receptors are also enhanced by hypoxia in embryonic chickens (73, 123), as well as enhanced sympathetic innervation in the peripheral vasculature (122). The mammalian fetal peripheral vasoconstrictor response to hypoxia, part of the fetal brain-sparing response and triggered by sympathetic activation, is also markedly sensitized by chronic hypoxia (117) and is greatly increased in the llama fetus relative to fetal sheep (101–103). Similarly, chronic hypoxia increases gene expression of β-adrenergic receptors in larval zebrafish (53) and increases cardiac responsiveness to adrenergic agonists in rainbow trout, as well as delaying the onset of cholinergic control (91). The sensitization of the sympathoadrenal medullary system by developmental hypoxia serves to increase oxygen delivery by raising cardiac output and also contributes to the brain-sparing effect through enhanced peripheral vasoconstriction. However, sustained sensitization can be detrimental and lead to cardiac and vascular remodeling and dysfunction, increasing cardiovascular risk in later life (12).

Mitochondrial Remodeling and Oxidative Stress

During normal development in mammals, a metabolic shift from anaerobic to aerobic respiration occurs during mid to late gestation and the heart relies predominantly on mitochondria for the majority of ATP production (124). Hypoxia is expected to reduce ATP production and increase reactive oxygen species (ROS) production, which can lead to mitochondrial remodeling (125). Indeed, early- and late-onset gestational hypoxia has been reported to decrease fetal cardiac mitochondrial protein expression and activity of electron transport chain complexes, increase ROS and markers of oxidative stress, reduce mitochondrial DNA copy number, and decrease mitochondrial respiration (126–128). Interestingly, the phenotype in all these studies was sex dependent and either absent in females or more pronounced in males. In contrast, the avian mitochondrial phenotype response to hypoxia is much milder, with one study finding no effects of hypoxia on chicken embryonic mitochondrial ROS production and respiration (apart from a mild decrease in complex IV) (129) and another finding an increase in mitochondrion-derived oxidative stress, together with a reduction in mitochondrial efficiency (130). To our knowledge, only one study has been performed on embryonic ectothermic mitochondria, which showed that hypoxia had no effects on alligator mitochondrial respiration or efficiency (131).

Effects of Developmental Hypoxia on the Adult Cardiovascular System

The seminal work from David Barker in the 1980s showed that intrauterine stressors could increase cardiovascular disease susceptibility in adulthood (132), a phenomenon known as developmental programming. Since then, there has been extensive research into the long-term effects of developmental hypoxia on cardiovascular health and disease. This section reviews the cardiovascular phenotype of vertebrates that were exposed to developmental hypoxia and subsequently maintained in normoxia until adulthood.

Long-Term Outcome in Birds and Mammals

It is now well established from epidemiological and laboratory studies that mammalian pregnancies complicated by hypoxia increase the incidence and likelihood of cardiovascular dysfunction and disease in adulthood (12, 133–136). After birth, the growth-restricted neonate continues to develop ex utero in a process called “catch-up growth” allowing for the rapid development of organs that were sacrificed in utero (137). Although necessary, the accelerated growth causes problems of its own and has been linked to programmed disease (138) The most common attributes of the cardiovascular phenotype of adult offspring from hypoxic pregnancies include cardiac hypertrophy, enhanced myocardial contractility, hypertension, endothelial dysfunction, thickening of the aortic wall, sympathetic dominance, mitochondrial abnormalities, and diastolic dysfunction (reviewed in Ref. 12). Many of these problems are carried forward from the hypoxic pregnancy, whereas others appear to develop with aging, and, similar to the embryonic phenotype, females are usually less affected than males. Although the cardiac phenotype is not always overt, it is important from a clinical perspective because it appears to sensitize the adult heart to disease stimuli, such as ischemia-reperfusion injury (109, 139–141). Indeed, recent clinical work has shown a higher incidence of many cardiovascular diseases in offspring from pregnancies associated with hypoxia, such as placental insufficiency, fetal growth restriction, and preeclampsia (133, 134, 136). These studies suggest that developmental hypoxia is an independent risk factor for cardiovascular disease, and studies are now underway to develop maternal therapies to prevent cardiovascular programming (12).

Unfortunately, far fewer studies have determined the long-term impact of developmental hypoxia on the adult avian cardiovascular system, but there are clearly many similarities with the mammalian phenotype. For example, sex-dependent pulmonary hypertension and right heart dysfunction were found in adult chickens raised from eggs incubated at high altitude, and this was associated with hypotension and lower systolic and diastolic arterial pressures (107, 142). Some studies have also found cardiac hypertrophy in adult chickens from hypoxic incubations (142), whereas others have not (71, 73), and there have also been reports of reduced contractility, extended relaxation times, myocardial fibrosis, systemic hypertension, decreased β-adrenergic sensitivity, and altered baroreflex sensitivity (107, 123, 143). Variations in the cardiovascular outcome of developmental hypoxia between studies are likely dependent on the specific experimental conditions, but these studies highlight the similarities between chickens and mammals in the cardiovascular responses and the programming of heart disease. Therefore, the chicken embryo continues to be a useful model for assessing the consequences of chronic developmental hypoxia in isolation, and it confirms that developmental programming of heart disease is not solely dependent on maternal and/or placental factors.

Long-Term Outcome in Reptiles

There are many similarities in the cardiovascular phenotype of reptiles and mammals subjected to hypoxia during development. For example, juvenile reptiles (1–

3 yr) from hypoxic incubations have an increased heart-to-body mass ratio, sympathetic dominance, and greater left ventricle stroke volume (76, 144–146). The increase in cardiac performance and adrenergic tone allows American alligators from hypoxic incubations to maintain higher aortic and carotid blood flows during swimming compared with their normoxic counterparts (144). Interestingly, the hypoxic alligators also had a decreased ratio of right ventricle to left ventricle mass (76), which is similar to adult mammalian offspring from hypoxic pregnancies and may reflect a sustained pulmonary hypertension (147, 148). Juvenile snapping turtles from hypoxic incubations also have increased stroke volume and cardiac output, but this is achieved by a different mechanism, since they have lower heart rates and a normal heart-to-body mass ratio (149). Similar to alligators, 5-yr-old turtles from hypoxic incubations have increased systemic blood flow (149). Nevertheless, in contrast to mammals, reptiles from hypoxic incubations do not show signs of diastolic dysfunction and, in fact, exhibit faster rates of ventricular relaxation (127). Another difference from mammals is that alligator hatchlings do not exhibit catch-up growth after hypoxia and instead remain growth restricted into adulthood (76, 144–146).

Some studies suggest that developmental hypoxia in reptiles can program greater hypoxia resistance later in life (145, 150). For example, exposure to developmental hypoxia blunts the cardiovascular response to acute hypoxia (4%O_2 for 20 min) in alligators (145) and allows juvenile snapping turtles to maintain cardiac output twofold higher than control animals during 2 h of anoxia (150). The improved anoxia tolerance in snapping turtles was supported by an increased myofilament calcium sensitivity (151), a superior ability to suppress cardiac myocyte ROS production during anoxia (151), and lower basal mitochondrial ROS production (152). This latter finding may have important physiological and ecological implications, because limiting ROS production during hypoxia will reduce the likelihood of oxidative stress damage, which could be especially important for freshwater turtles that regularly encounter anoxia during breath-hold dives and when they are overwintering under ice-covered lakes. Similar adaptive responses have also been observed in adult American alligators after developmental hypoxia, where hypoxic cohorts have enhanced mitochondrial efficiency through a reduction in proton leak respiration (131).

Long-Term Outcome in Fish

The cardiovascular phenotype of juvenile and adult fish from hypoxic incubations is very poorly studied. Some fish exposed to developmental hypoxia exhibit catch-up growth (99, 153, 154), whereas others do not (93, 155), but to our knowledge there is nothing known about cardiac structure or function. There is evidence that developmental hypoxia alters cardiac gene expression in rainbow trout, which could

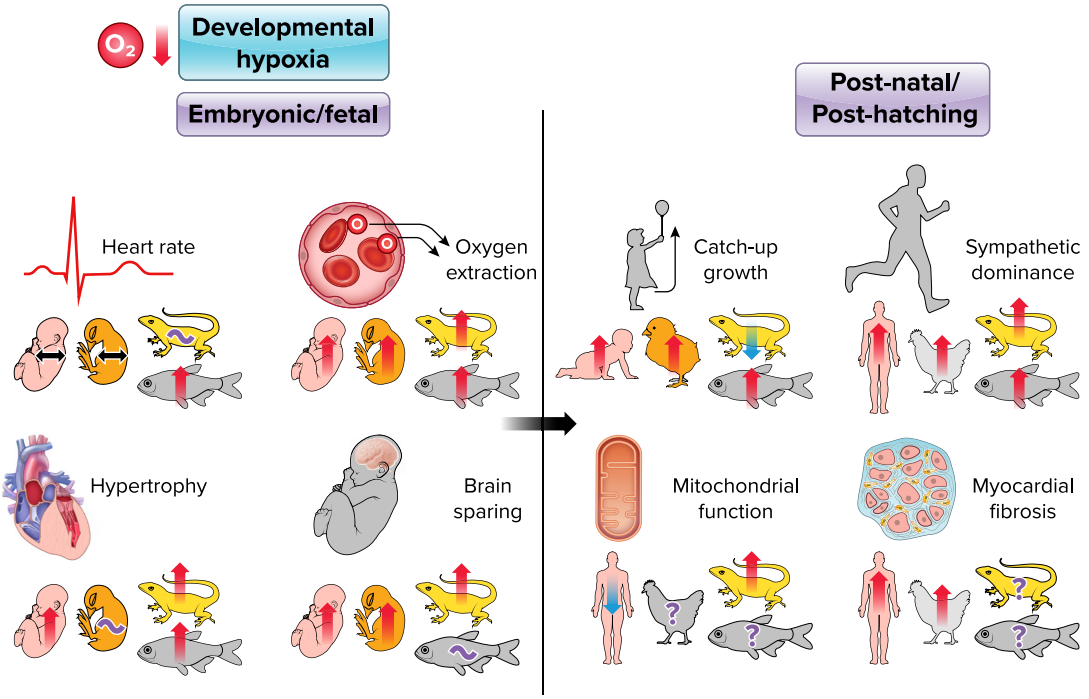

FIGURE 1. **Summary of effects of chronic developmental hypoxia (ranging between days and months) on the cardiovascular system during fetal and postnatal life across species**
Downward- and upward-facing arrows represent a decrease or increase in the factors, respectfully. A tilde represents contrasting evidence within the literature, and question marks represent a currently unknown response to developmental hypoxia. Image created with BioRender.com, with permission.

have implications for contractile function (154), and critical swimming speed is reduced (154). However, another study found negligible effects of developmental hypoxia on aerobic scope in Atlantic salmon (156). In contrast to reptiles, some fish that are raised in hypoxia show a reduced hypoxia tolerance as juveniles (99, 153). Clearly, more studies are necessary to fully determine the long-term impact of embryonic hypoxia exposure on fish cardiovascular function and fitness.

Perspectives

Despite the profound differences in developmental morphology and physiology among vertebrates, there are remarkable similarities in the cardiovascular responses to chronic developmental hypoxia (FIGURE 1). These similarities are even more impressive when one considers the differences between studies in experimental variables, such as species, body temperature, severity of hypoxia, and physiological status (e.g., carbon dioxide levels and metabolism). This suggests that the main cardiovascular responses to developmental hypoxia have ancient origins and have been well conserved throughout vertebrate evolution. However, these compensatory responses early in life may claim trade-offs later in life. In mammals and birds, developmental hypoxia is associated with cardiovascular dysfunction and increased susceptibility to ischemia-reperfusion injury. The clinical implication for humans is that chronic developmental hypoxia should be recognized as an independent risk factor for offspring cardiovascular disease. In contrast, although reptiles and fish that experienced hypoxia during development share some common traits with mammals in adulthood, there are no overt signs of cardiovascular disease, and some species may even have enhanced stress tolerance. The reasons for the differential adaptation to developmental hypoxia in vertebrate endotherms compared with some vertebrate ectotherms are not clear. It is possible that ectothermic vertebrates elicit compensatory responses to hypoxia during development that do not claim adverse consequences at hatching. These alternative compensatory responses may include actions that lower metabolic demand, such as the neuronal hypometabolism reported in the llama fetus. Nevertheless, even if disease does not manifest, changes in the cardiovascular phenotype of ectotherms in response to developmental hypoxia can impact survival by altering fitness-related behaviors, such as mate selection and predator-prey interactions. Future research in this field may consider designing experiments that isolate the beneficial effects of developmental hypoxia on cardiovascular health from detrimental effects, as well as measuring fitness-related traits such as fecundity and mortality. It is also important to define the threshold level and duration of developmental hypoxia that elicits changes in the vertebrate cardiovascular system, as this will help to predict clinical outcomes and the effects of climatic disturbances. Finally, more work needs to be done to understand the synergistic effects of developmental hypoxia and other environmental factors that often occur simultaneously, such as hypercapnia and acidosis. Taking this kind of integrative approach is critical for predicting and mitigating the effects of climate change on the developmental plasticity of birds and ectothermic vertebrates. ■

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