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Review

Developmental trajectories, critical windows and phenotypic alteration during cardio-respiratory development☆

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ABSTRACT

Embryo-environment interactions affecting cardio-respiratory development in vertebrates have been extensively studied, but an equally extensive conceptual framework for interpreting and interrelating these developmental events has lagged behind. In this review, we consider the conceptual constructs of "developmental plasticity", "critical windows", "developmental trajectory" and related concepts as they apply to both vertebrate and invertebrate development. Developmental plasticity and the related phenomenon of "heterokairy" are considered as a subset of phenotypic plasticity, and examples of cardio-vascular, respiratory and metabolic plasticity illustrate the variable outcomes of embryo-environment interactions. The concept of the critical window is revealed to be overarching in cardio-respiratory development, and events originating within a critical window, potentially mitigated by "self-repair" capabilities of the embryo, are shown to result in modified developmental trajectories and, ultimately, modified adult phenotype. Finally, epigenetics, fetal programming and related phenomena are considered in the context of potentially life-long cardio-respiratory phenotypic modification resulting from embryo-environment interactions.

1. Introduction

Cardio-respiratory development in vertebrates has long been of interest, from Aristotle's vivid descriptions of the onset of heart beat and development of the vasculature of the chicken embryo, through William Harvey's view that the heart arises from a drop of blood, to late 20th century views of heart canalization. Yet, technical limitations on physiological measurements, together with only a fragmentary understanding of embryonic physiological development, leaves many areas of development of the cardio-respiratory system open to investigation by developmental physiologists. Among the most intensely investigated areas are those investigating how and to what extent developmental processes of the heart, vasculature and respiratory structures can be modified by environmental and other perturbations (e.g. West-Eberhard, 2003; Spicer and Burggren, 2003; Kiserud, 2005; Reeves and Gozal, 2005; Spicer and Rundle, 2007; Warkentin, 2007; Domyan and Sun, 2010). What are the environmental cues that modify cardio-respiratory development? Are there graded effects on the circulatory and gas exchange systems? What are the self-repair capabilities of organ systems that temporarily diverge from their normal developmental patterns?

Many of these questions, and a myriad of others, fall under the constructs of "developmental plasticity", "critical windows", "developmental trajectory" and related concepts. In this review, we explore these concepts. Some of them are well supported by extensive experimentation (e.g. developmental plasticity), whereas in others, we are only beginning to explore their full depth and potential impact (e.g. epigenetics, fetal programming). Our intent, then, is to not fully review the data, but rather to use selected examples to more clearly reveal the significance of these concepts in the developmental physiology of the cardio-respiratory systems.

2. Concepts in modification of cardio-respiratory development: theory and practice

2.1. Developmental plasticity of the cardio-respiratory systems

"Phenotypic plasticity" refers to the capability of an organism to modify its phenotype in response to environmental changes. While most biological processes are of course plastic, phenotypic plasticity is viewed as a modification of phenotype that ultimately is constrained by a genotype X phenotype environment, which defines a series of reaction norm at the individual, population and species levels (for review see Hutchings, 2011). Phenotypic plas-

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ticity is also viewed as a heritable trait that can involve so-called "plasticity genes" (e.g. Loebrich and Nedivi, 2009; Zhang and Ho, 2011)

As a concept phenotypic plasticity is well entrenched in the cardiovascular and respiratory physiological literature (e.g. Pigliucci, 2001; Carroll, 2003; Swynghedauw, 2006; Garofalo et al., 2009; Storz et al., 2010), although some controversy remains around the influence and impact of phenotypic plasticity (e.g. Pigliucci et al., 2006), Phenotypic plasticity of the adult heart, for example, is evident in the cardiac remodeling and/or organogenesis that occurs in response to stressors such as mechanical overload or nutrient starvation due to myocardial infarction (e.g. Bonnet, 1996; Swynghedauw, 2006). Phenotypic plasticity in structures for gas or ion exchange is evident in morphological changes to the lungs of birds and mammals at high altitude (Storz et al., 2010) or as a response to pulmonary artery hypertension (Sakao et al., 2010). Similarly, the morphological features of gills of adult fishes are viewed as quite plastic, and can be remodeled in response to environmental toxins or hypoxia (Sollid and Nilsson, 2006). Remodeling of cardiovascular and respiratory structures is usually viewed as compensatory (e.g. enhanced surface area in response to hypoxia) and may or may not be reversible (see below).

While phenotypic plasticity is often framed in the context of changes in morphological and physiological phenotype, there is also strong evidence for environmentally driven plasticity of biochemical phenotype, which may have direct effects on metabolic rate, likely acting through enzymes or energy sources that may directly affect metabolic rate. For example, in the teleosts cichlid fish *Cichlasoma amazonarum*, chronic hypoxic exposure induces changes in the LDH isozyme profiles of the heart, liver and brain, leading to enhanced hypoxic tolerance (Almeida-Val et al., 1995). Oxidative ATP production is highly plastic in poikilothermic animals (e.g. fishes, reptiles) exposed to different thermal regimes mimicking climates with variable thermal regimes (Seebache et al., 2010), with the limits to such plasticity delineated by production of reactive oxygen species, mitochondrial substrates and membrane proton leaks. Even in homeotherms such as the wild rat, *Rattus fuscipes*, LDH and enzymes controlling oxidative metabolism (citrate synthase, cytochrome *c*-oxidase) as well as mitochondrial oxygen consumption are affected by body temperature fluctuations (Glanville and Seebacher, 2010)). Skeletal muscle of vertebrates also shows considerable metabolic phenotypic plasticity, with enhanced contractile activity (Hood et al., 2006) or changes in temperature regimes (Johnston and Temple, 2002) leading to altered metabolism via changes in muscle mitochondrial volume, changes in myosin ATPase activity, myosin heavy chain composition, and numerous other factors. Collectively, these data indicate that phenotypic plasticity is not related to just morphological and physiological traits, but applies to metabolism and its supporting processes as well.

Phenotypic plasticity is also a concept highly applicable to developmental physiology. Indeed, "developmental plasticity" can be viewed as a specific embryo-based subset of phenotypic plasticity. Developmental plasticity is generally defined as the modification of the normal developmental plan typically as a result of embryo-environment interactions. Cardiovascular developmental plasticity has been shown repeatedly in all vertebrate classes, and comprises changes in the morphology of the heart and vessels with concomitant changes to the derivative processes generating organized convective blood circulation (for reviews see Barker, 2004; Jones et al., 2006; Pelster et al., 2010). Recently, Kopp et al., 2007 have shown in the larvae of zebrafish (*Danio rerio*) that experimentally induced isovolemic anemia, and the attendant changes in hemodynamic shear forces, result in cardiac remodeling (increased ventricular volume) as early as day 7 post fertilization, demonstrating that developmental plasticity appears early in development. Developmental plasticity is also evident in gas exchange organs, including mammalian lungs (Tournier et al., 1992) and the gills of amphibian larvae and fishes (Burggren and Mwalukoma, 1983; Craig et al., 2007; Rogge and Warkentin, 2008; Crispo and Chapman, 2010). Moreover, the regulatory systems that modulate performance of cardio-respiratory structures are also subject to shaping by environmental factors (e.g. Simard et al., 2003; Bavis and Mitchell, 2008; Ferner and Mortola, 2009). Finally, metabolic plasticity is stimulated by early developmental challenges from hypoxia, temperature and other factors (e.g. Dzialowski et al., 2002; Watkins et al., 2008; Reyna, 2010). Inadequate embryonic or fetal nutrition is also a contributing factor, and is being evoked to describe a multitude of adult onset pathologies and compensatory responses in humans (for reviews, see Burdge and Lillycrop, 2010; Kanaka-Gantenbein, 2010; Wells, 2011).

Relatively few studies have explored the reversibility of morphological or physiological features arising through phenotypic plasticity. In one of the more extreme examples, some invertebrates show the environmentally driven reversal of the entire body morph, transitioning from initial polyp to medusa and back again in Hydrozoans (Bavestrello et al., 2000). Reversibility of developmental plasticity has been demonstrated in renal structures (Gabella and Uvelius, 1994; Sweeney et al., 2008) and in vascular smooth muscle of both developing and mature animals (Moiseeva, 2001; Owens, 2007; Cooley et al., 2010)

Finally, it is important to note in the discussion of phenotypic plasticity that there is some conceptual overlap between that concept and "epigenetics". While trying to avoid semantic digressions, suffice it to say that the phenomenon of phenotypic plasticity is usually viewed as applicable to individuals during their life span, whereas the term "epigenetics" typically involves *transgenerational* phenotypic modification (e.g. Ho and Burggren, 2011 and see below).

In summary, the entire gamut of organizational levels, from molecules to organ systems, appears plastic to variable degrees, and the plasticity of responses to environmental challenge is often enhanced when evoked in early life stages.

2.2. Heterokairy in cardio-respiratory systems

Developmental plasticity, described above, is not just a change in the overall developmental plan and eventually the emergent adult phenotype, but can also involve the relative and/or absolute movement of specific developmental landmarks forward or backward in development on an individual- or population-level scale. This phenomenon, termed "heterokairy" (e.g. Spicer and Burggren, 2003; Spicer and Rundle, 2007; Warkentin, 2007), must be differentiated from "heterochrony", which is change in the timing of developmental events over evolutionary time, between species (Hall, 2003; Smith, 2003). One of the earlier demonstrations of respiratory physiological heterokairy of the gas exchange, circulatory and metabolic systems was provided by Spicer and El-Gamal (1999), who showed that development under hypoxic conditions accelerates the first appearance of the capacity for regulating oxygen uptake in the brine shrimp *Artemia franciscana*. Tills et al. (2010) described heterokairy in the development of the circulation of the freshwater snail *Radix balthica*. Development under hypersaline conditions resulted in delayed onset of heartbeat, as well as changes in the timing of the appearance in development of eye spot formation and foot attachment. The development of respiratory morphology and physiology can also be affected by biotic as well as abiotic conditions. For example, predation pressure during larval development in the red-eyed tree frog delays gill regression even as development otherwise proceeds normally (Warkentin, 2007).

Heterokairy presents a powerful lens through which to view the interactions of embryo-environment interaction in a variety

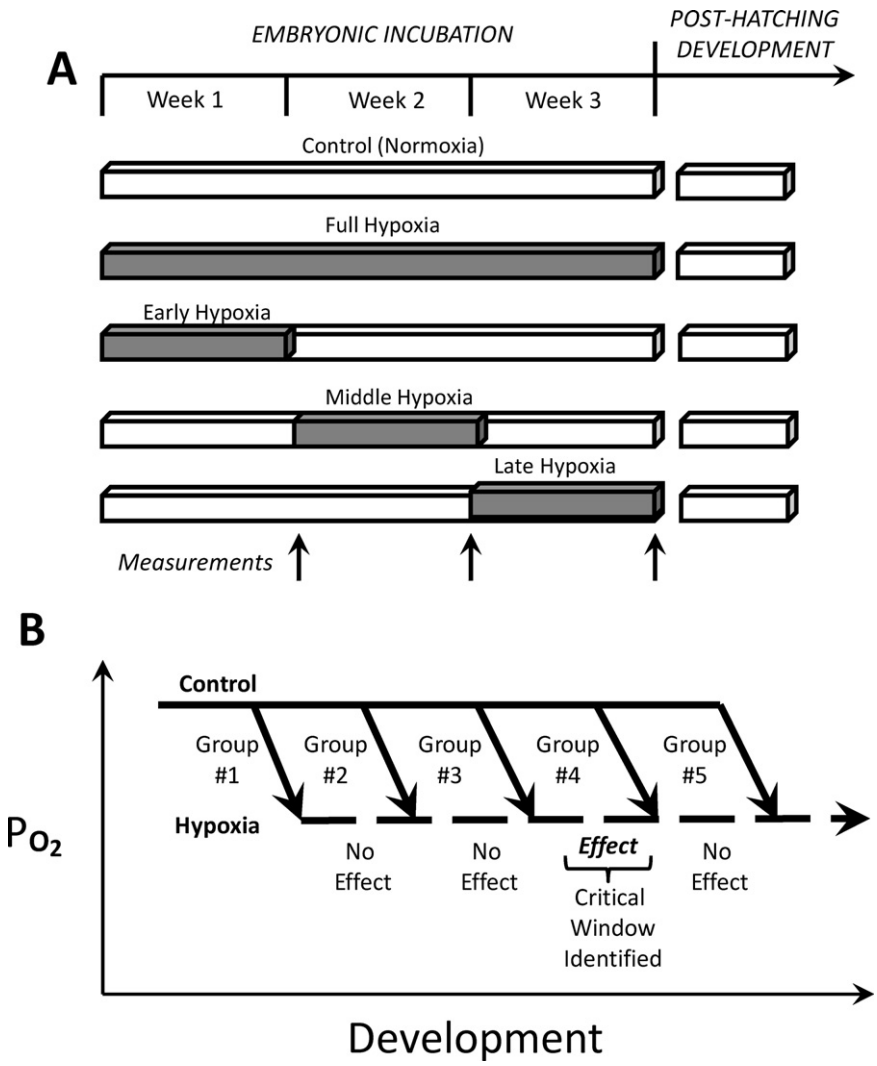

Fig. 1. Typical experimental protocols designed to use hypoxic exposure to reveal critical windows for cardio-respiratory development during the ~21-day incubation period for chicken embryos. (A) Protocol to identify boundaries of critical windows. Arrows indicated timing of physiological or morphological measurements. (B) Exposing multiple populations to hypoxia at different times in development can define the beginning and end of a specific critical window. In this hypothetical example, the critical window begins and ends in the C–D developmental interval.

of developing animals. This phenomenon may also account for a significant proportion of study-to-study variations in basic observations of physiological development of the cardio-respiratory and other organ systems.

2.3. Critical windows for cardio-respiratory systems

Interpretation of plasticity in a physiological context also requires appreciation of the venerable concept of "critical windows" for development – that period of time for a particular tissue, organ, or organ system when it may experience a suite of morphological and physiological modifications in response to an abnormal environment for development (e.g. Burggren, 1998; Nijland et al., 2008; Loepke, 2010). Such modifications typically reduce fitness and sometimes prove fatal.

While development of an organism is highly directed by a genetic template, development is nonetheless susceptible to the surrounding environment in complex, wide-reaching and sometimes unpredictable ways. Often such susceptibility becomes evident in the sometimes tedious process of mapping of critical windows for development. Such mapping has occurred largely in the context of human medicine, often revealed through epidemiological studies, as in the tragic case of thalidomide induction of limb defects in humans (Knobloch and Rüther, 2008), the early origins of atherosclerosis (Singhal, 2009), or the impact of environmental chemicals on lung development (Miller and Marty, 2010). However, the duration and developmental impact of critical windows during development can also be revealed using experimental approaches in the laboratory with appropriate developmental models. For example, studies of avian embryonic development, a highly developed model for early cardiovascular development, have created protocols specifically for determining the critical windows of cardio-respiratory development (e.g. Dzialowski et al., 2002; Chan and Burggren, 2005) (Fig. 1A). Such protocols are readily adapted to a variety of environmental stressors or incubation/development periods. In theory (though more difficult in practice), the periods of environmental perturbation, immediately followed by sampling at the end of the exposure period, could be reduced to the level of days or even hours, thus defining both beginning and end of a critical window for a specific morphology or physiological process (Fig. 1B).

Using the form of protocol described above with hypoxic/hyperoxic exposure as the environmental perturbation, critical windows (or the lack thereof) have been identified in avian embryos with respect to several aspects of cardio-respiratory and metabolic physiology. In the domestic chicken *Gallus domes-*

ticus, hatchlings had lower oxygen consumption when exposed to chronic hypoxia during the middle period of embryonic incubation (days 6–12), but not when chronically exposed from days 1 to 6 or 12 to 18 (Dzialowski et al., 2002). This study also demonstrated critical windows for the critical PO_2 (P_{crit}) for oxygen consumption. Yet, hematocrit and blood hemoglobin concentrations were unaffected, suggesting differential dosage thresholds for hypoxic effects within potential critical windows for development. In a separate study, development of the chorioallantoic membrane, skeletal structures and the eye all showed variable timing and length of critical windows, as evident from their developmental vulnerability to chronic hypoxia (15% O_2) (Chan and Burggren, 2005). Interestingly, however, neither the heart nor lungs were affected at any stage of development by this level of chronic hypoxia applied in the first, second or third week of embryonic development. Critical windows for cardiac development also occur at cellular and molecular levels. For example, in the rat there is a critical window for cardiomyocyte genome duplication and myocyte growth, exposed by induction of cryptosporidial gastroenteritis, that coincides with the developmental transition from proliferation to hypertrophy (Anatskaya et al., 2010). Using iron-deficiency as a challenge in post-implantation embryonic rats, the period of organogenesis was identified as a crucial critical window for cardiomyocyte hypertrophy (Andersen et al., 2006).

Critical windows have also been observed for pulmonary development. In an examination of ventilatory responses to hypoxia at various points in chicken embryo development, Ferner and Mortola (2009) showed that prenatal hypoxia blunts pulmonary ventilation chemosensitivity in hatchlings, presumably by disruption of the normal development of the carotid bodies. In chicken embryos, chronic exposure to 17% O_2 accelerates surfactant lipid maturation (Blacker et al., 2004). Considerable evidence of critical windows for lung morphological development has also been gathered in mammals (including humans) in the context of exposure to environmental chemicals, including tobacco smoke (e.g. Wang and Pinkerton, 2008; Miller and Marty, 2010).

No discussion of critical windows for cardiovascular, pulmonary, renal and other systems is complete without the mention of "fetal programming" and disease states. Fetal programming has been described as "*the process whereby a stimulus or insult at a critical period of development has lasting or lifelong effects*" (Barker, 2000), and essentially represents the implications in later, adult life of developmental disturbances induced during critical windows for development. Basic scientists and clinicians alike have recognized fetal programming as an exciting frontier in both developmental physiology and the etiology of adult human disease with fetal origins. Indeed, both human adult and childhood diseases with profound public health implications have been linked to suspected disturbances occurring specifically in the fetal environment. Prominent among these are kidney disease, hypertension, coronary heart disease, obesity, non-insulin dependent diabetes, and osteoporosis (Barker, 2000; Marchand and Langley-Evans, 2001; Barker, 2004; Alexander, 2006; Patterson and Zhang, 2010). These effects are often linked to low birth weight (LBW) (Rasch et al., 2004; Alexander, 2006).

Finally, let us address the important question "*When do system-specific critical windows generally appear in development*"? Indeed, the concept of critical window may be as fundamental to development as cell division. For example, pre-implantation mammalian embryos subjected to variations in handling and culture may experience altered patterns of gene expression, cell division and morphology (Watkins et al., 2008), presumably the result of a combination of epigenetic, cellular, and metabolic mechanisms. Similarly, fertilized eggs of the Northern bobwhite quail (*Colinus virginianus*) exposed to different thermal regimes prior to any egg incubation subsequently produced embryos with different whole

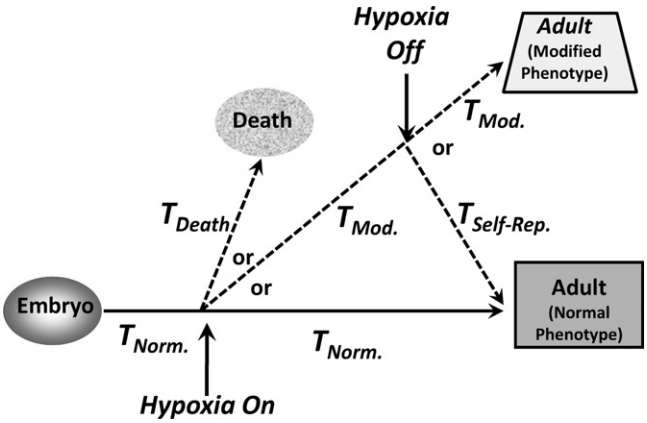

Fig. 2. The concept of developmental trajectories, using hypoxia as an example of a stressor in hypothetical embryo-environment interactions. T_{Death} = trajectory leading to immediate death of embryo. $T_{Mod.}$ = modified trajectory potentially leading to a modified adult phenotype. $T_{Self\text{-}Rep.}$ = trajectory reflecting "self-repair" capability leading normal adult phenotype. See text for additional description. (After Burggren and Fritsche, 1997.)

embryo oxygen consumption rates on Day 10, although these effects were reversed (repaired) with further development (Reyna, 2010). Embryonic mortality was also affected by pre-incubation thermal storage conditions in this study.

2.4. Developmental trajectories and the cardio-respiratory systems

Given that the development of an animal, organ system, organ or tissue follows a potentially complex and variable pathway, the notion of "developmental trajectory" – quite simply the potentially variable pathways in development that an animal takes – becomes a useful paradigm with which to view development (e.g. Burggren, 1998, 1999; Maughan, 2005; Chennault and Podrabsky, 2010; Dixon, 2010). Again, conceptually simple protocols exist to determine how a given variable, such as heart or lung development, moves through time and space towards the end-target of the adult phenotype. Indeed, the same protocols that identify critical windows can yield data that can be used to create developmental trajectories. Fig. 2 shows a hypothetical series of potential developmental trajectories related to a period of hypoxic exposure. The normal developmental trajectory ($T_{Norm.}$) leading to a normal adult phenotype (e.g. normal heart mass) may be unaltered by hypoxic exposure if: (1) the exposure falls before or after a critical window or (2) the magnitude of the exposure falls before the innate threshold for a response. However, if the hypoxia stimulus falls *within* a critical window, several outcomes are possible. Of course, the embryo may die (T_{Death}) if the hypoxic exposure is sufficiently severe. If the embryo survives, its subsequent heart development may be diverted along a modified developmental trajectory ($T_{Mod.}$) towards what will ultimately resulted in a modified adult phenotype.

A key issue when examining modified developmental trajectories involves whether the embryo, larva or fetus is capable of "self-repair". That is, is the developing animal simply a slave to the abnormal developmental trajectory that it is pushed towards by the "wrong" environment at the "wrong" time? Putting this differently, if the embryo's normal development is modified by an environmental stimulus appearing during a critical window for development, is that modification permanent, or is there sufficient phenotypic plasticity such that the modification can be reversed or otherwise altered with another change in environment?

To examine the notion of self-repair, consider how different outcomes may emerge upon removal of the hypoxic stimulus and

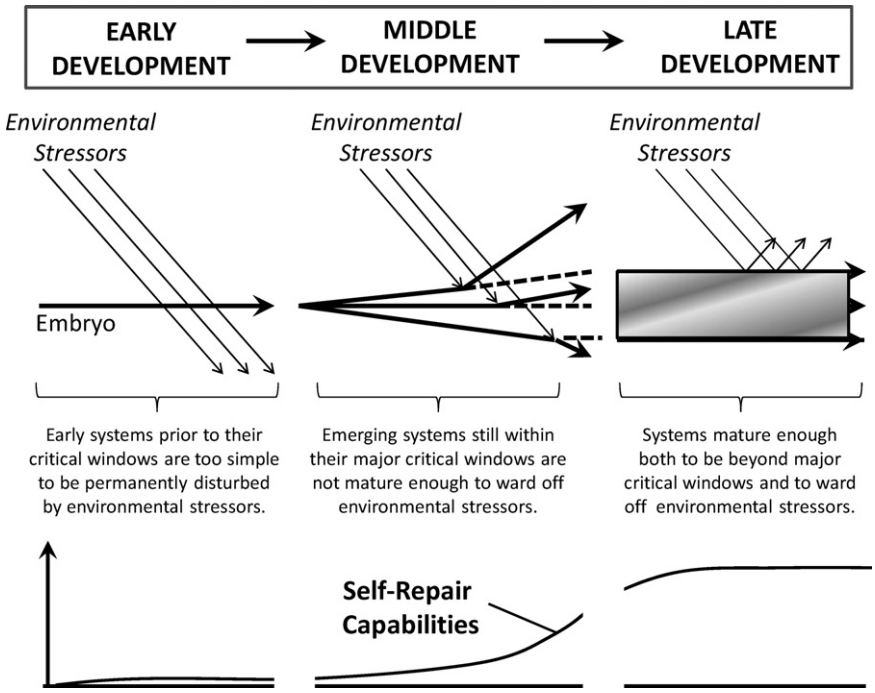

Fig. 3. An interpretation of the causes for variable effects of environmental stressors on developmental processes, presented as reaction norms for early, late and middle stages of ontogeny.

its cardiac effects in our hypothetically developing animal. First, the immature animal may continue on T_{Mod}, leading to modified ventricular mass in the adult because it lacks sufficient self-repair capabilities. Alternatively, it may move along a novel trajectory ($T_{Self\text{-}Rep.}$), reflecting a "self-repair" capacity. If the capability for cardiac self-repair is sufficiently large, the animal might actually end up with a normal adult heart phenotype despite a convoluted developmental trajectory earlier in development. Relatively few studies have considered self-repair of specific organ systems (e.g. heart, lungs). However, recovery from general body mass reduction induced by hypoxic exposure has been documented in chickens during development. Exposure to 15% hypoxia from days 6 to 19 of incubation (Villamor et al., 2004) or during the entire incubation period (Zoer et al., 2009) led to reduced body mass measured at embryonic day 19. Remarkably, however, the embryos in both of these studies recovered body mass to a level not significantly different from controls just two days later at the time hatching. Different but equally interesting findings were reported by Ruijtenbeek et al. (2003), who indicated that chicken embryos exposed to 15% hypoxia during incubation did indeed have reduced body mass at hatching, but by 14–15 weeks of post-hatch breathing of air the juveniles had regained mass to a level not different from that of controls. The likelihood of any particular developmental trajectory actually occurring and whether it reflects self-repair capability depends heavily, of course, upon *when* in development the environmental stimulus actually begins and ends – i.e. whether a critical window exists for a modified developmental trajectory. Thus, even subtle differences in such time courses for exposure could account for variations in the literature.

Focusing more strictly on cardio-respiratory systems, studies of embryonic respiratory and cardiac development in the embryo of the chicken *G. domesticus* examined variables ranging from mass of heart and other organs to oxygen consumption (e.g. Dzialowski et al., 2002; Chan and Burggren, 2005). Their data suggest to us three general phases regarding susceptibility and self-repair capacities during development (Fig. 3). Early in development, organ systems may be vulnerable to developmental perturbations due to critical windows for development, but unless they occur precisely during critical periods for development (or if they do not rise above a critical threshold within the window), the early embryo may in most instances simply be too immature to suffer permanent damage, especially since most of the time period for development may remain for self-repair mechanisms to be evoked. Alternatively, late in development, systems are sufficiently developed and physiological, cellular and molecular regulatory mechanisms may be sufficiently mature to fend off environmental challenges, or at least repair the effects of such challenges. Thus, the mid-developmental periods could be the most vulnerable over-all. A hypothetical system at this mid-point has developing morphology and physiology that can be seriously altered, yet has neither the regulatory capabilities to fend off environmental challenge *nor* enough time left in embryonic development for self-repair to occur.

While the conceptual construct above is useful for interpreting experimental results on embryo-environment interactions, we return to the study of Watkins et al. (2008), showing that even pre-implantation embryos could be susceptible to modified developmental trajectories if subjected to sufficiently profound environmental stressors. Thus, the scheme presented in Fig. 3 represents the reaction norms, rather than all possible outcomes.

Rich in conceptual components and potential applications, actual demonstrations of discrete developmental trajectories in physiological development are scarce. By the end of April, 2011, there were less than 50 papers in the Pub Med data base (http://www.ncbi.nlm.nih.gov/pubmed) that even contained the phrases "cardiovascular developmental trajectory" or "metabolic developmental trajectory". When one integrates (1) the concept of developmental trajectory together with (2) the notion of critical windows during which trajectory changes can be evoked by environmental disturbance, then the true complexity of embryo-environment interactions begins to emerge. Moreover, profound dose-response effects will very likely affect each of these phenomena during development. Clearly, creating protocols using simple animal models will be an extremely productive area for future cardio-respiratory developmental research.

3. Caveats, applications and new avenues for research

Embryo-environment interactions and the insights into critical windows and developmental trajectories that lie within these interactions are ripe for future exploration. Yet, developmental physiologists must also be aware of several caveats as they move forward with their experiments, as we will now consider.

3.1. Transferability of data

A question that frequently, and appropriately, arises when examining data from studies on lower vertebrate and even invertebrate studies is "How transferable/generalizable are the findings across animals"? Putting it differently, "Does a determination of a critical window for heart development in larval anuran amphibians have relevance to understanding what might apply in the embryos/fetuses of homeotherms or vice versa"? The unequivocal answer is . . ."Maybe". Certainly demonstrating that heart development is susceptible to oxygen levels at particular times in development in one vertebrate will strongly signal that, in qualitative if not quantitative terms, that this is likely to be a general vertebrate trait. This can be said with some degree of confidence because of the repeated demonstration of common mechanisms for early cardiovascular development, beginning at the molecular level, that are independent of the specific cardiac and vascular circuitry that ultimately appears in the adult morph (e.g. Burggren, 1998; Bishopric, 2005; Boogerd et al., 2009; Pérez-Pomares et al., 2009; Crossley and Burggren, 2009).

Even some quantitative aspects of early cardiovascular and metabolic development are comparable. For example, the early pressures and flows generated by the heart of the African clawed frog *Xenopus laevis* (Hou and Burggren, 1995a,b) and the domestic chicken *G. domesticus* (Tazawa and Hou, 1995) are surprisingly similar in the hours and days following first onset of heart beat. Yet, as cardio-respiratory systems begin to mature in the embryo/larva/fetus, the inevitable anatomical and physiological differences characteristic of the various adult morphs of vertebrates begin to appear as well. Thus, the transferability of findings is greatest early in ontogeny, and likely diminishes as development continues. Fortunately, this early transferability of data from lower vertebrates or avian embryos coincides with the developmental period in mammals when some physiological measurements are most difficult or even impossible to obtain due to the embryo's or fetus' confinement within the placental environment. For example, while blood flow in mammals can be tracked throughout development with Doppler imaging, the earliest blood pressure measurements in fetal sheep (a routine model for mammalian fetal physiology) are typically made no earlier than about 1/3 of the way through gestation (e.g. Eghtesady et al., 2007), and experimental intervention such as injection of agonists/antagonists is extremely difficult in the first trimester. Thus, our knowledge of the onset of function, as opposed to the maturation of function, is likely to come from lower vertebrate and avian models for some time to come.

3.2. The "real" environment—a multi-variable setting

Another confounding aspect of studying embryo-environment interactions during development relates to our typical, time-honored approach to experimentation, wherein we fix all variables save for one which is manipulated experimentally to observe any induced effects. Unfortunately, the natural environment does not work that way. Rarely, for example, does only oxygen level vary, while carbon dioxide levels, temperature, light, etc. stay constant. Indeed, the natural environment for animals with "free-standing" embryos or larvae represents a highly complex pattern of concurrent change in multiple variables. Even embryos and fetuses of placental mammals experience a surprising range of conditions during their development related to nutrition, oxygen availability and disease states (e.g. Thornburg et al., 2008; Langley-Evans, 2009). Doubtlessly, many more subtle and nuanced effects of environment on development will only be revealed by looking at multi-variable modifications of developmental environments.

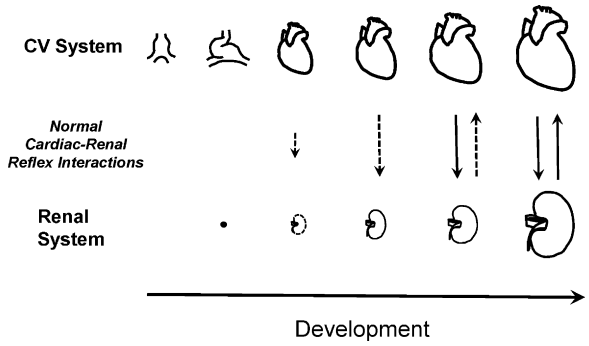

Fig. 4. The hypothetical ontogeny of cardiovascular-renal interactions in the developing vertebrate. Typically, the heart appears and begins to function in advance of the kidneys (left). In this scheme, then, the initial regulation is assumed to be cardiovascular over renal (middle). Soon, however, there are likely to be developing regulatory interactions between both systems, culminating in the full, complex, bilateral control typical of adults (right).

3.3. Multi-organ system interactions

In the same way that we have just emphasized the multi-variable nature of the "real" environment in which an organism develops, we must also emphasize the "real" multi-system nature of the developing organism. Although we almost invariably study organ systems in isolation from one another (even in the design of our *in vivo* experiments), the reality is that organ systems are constantly interacting and influencing the behavior of other systems. Consider, for example, the inextricably interwoven functions of the cardiovascular and renal systems, both in health and disease (for reviews see White et al., 2011; Merhaut and Trupp, 2010; Iwanaga and Miyazaki, 2010). The renin-angiotensin system (RAS) exhibits enormous influence over the cardiovascular system via direct and indirect hormonal signals (for reviews see Harrison-Bernard, 2009; Kumar et al., 2009; Rohini et al., 2010; Nguyen, 2010), just as the kidneys are utterly dependent upon appropriate blood flow for plasma filtration and urine formation (for reviews see Daniels and Maisel, 2007; Patel, 2009). We know a great deal about the mechanisms and effects of these interactions in adult animals, how do these physiological interactions (as distinct from the morphologies that support them) first appear and mature? The heart begins to develop and is functionally established well before the kidneys in vertebrates. Thus, early in development there can be no renal-cardiac interactions (Fig. 4). We may reasonably suppose, in addition, that the more mature heart begins to exert control over the pronephros and then mesonephros during embryonic develop *without* a corresponding regulation of cardiovascular function. Finally, in late development, we might conjecture that the two way interaction between the cardiovascular and renal systems, characteristic of juveniles and adults, is present and, if not fully developed, at least established. The description of cardiac-renal interaction presented above is, however, conjecture awaiting experimental exploration, but who will be drawn to such studies? Our training as physiologists typically has us focusing on single system, or one organ within a single system, and we further try to look at one variable at a time. Yet, our major breakthroughs in the future are likely to involve multi-system, multi-variable experiments. Such approaches will be aided both by the increasing trend

for collaborative teams composed of a wide range of experts, and also by the explosive acceleration of computing power and the average researcher's access to it.

3.4. Epigenetics: both a threat and an opportunity

Another confounding influence in developmental studies involves the burgeoning field of epigenetics. While epigenetic influences on physiological processes have been appreciated for decades, the potential impact of epigenetic phenomena on developmental physiology studies is just beginning to come to the forefront. A description of how, when, where and why physiological processes can be altered *across generations without changes in gene sequence* (essentially, the definition of "physiological epigenetics), is beyond the scope of this review. Briefly, however, dozens of studies have categorized the transgenerational transfer of physiological traits, range from tolerance to dehydration and hypoxia to metabolic rate and glucose metabolism, in some cases, over multiple generations (see reviews by Wolf and Wade, 2009; Ho and Burggren, 2011). While relatively few of the transgenerational effects catalogued in these articles specifically involve cardio-respiratory phenomena, there clearly are epigenetic influences in this area of physiology. Perhaps some of the most interesting (and potentially worrisome) physiological transgenerational effects involve the modification of embryo/larval physiology as a result of experiences of the parents (e.g. exposure to hypoxia, temperature change). In a series of epigenetic experiments using zebrafish (*D. rerio*), Ho (2008) exposed male and female adults to 1 to 4 weeks of hypoxia, before returning them to normoxia, where they were subsequently bred. Their offspring were then acutely exposed to severe hypoxia ($PO_2 \sim 30$ mmHg), and their susceptibility to hypoxia was assessed by determining the time to loss of body position equilibrium. Larvae had a significantly greater resistance to this first-time hypoxic exposure if their adult *parents* had been previously exposed to hypoxia, suggesting a non-genetic signal was crossing generations.

Epigenetic phenomena can also influence developmental plasticity, underscoring the complexity of the embryo-environment interactions. For example, avian and reptilian mothers place hormones and other modulating substances into the yolk of their eggs, with such deposition sometimes related to stressors experienced by that mother (Groothuis and Schwabl, 2008; Hamlin et al., 2010). This so-called "maternal effect" (sometimes called a "yolk effect") can result in maternal experiences affecting the cardiovascular physiological phenotype of the developing embryo. As an illustration, heart rate in various strains of the embryos of the domestic chicken (*G. domesticus*) grown in culture is altered by the yolk environment on which the embryo is grown (Fig. 5). Thus, day two embryos of broiler chicken strains developing on broiler yolk culture medium had higher heart rates than layer chicken embryos developing on the same culture medium. At the same time, heart rate of layer embryos was unaffected by development on broiler yolk culture medium (Ho et al., 2011). Thyroid hormone and yolk testosterone are suspected to be the yolk agents modifying embryonic heart rate. Moreover, in a series of xenobiotic experiments, heart rate of layer chicken embryos grown on the yolk culture medium of bird species with eggs ranging in size from 14 g (quail) to 1661 g (ostrich) showed a positive correlation with egg mass (Ho, 2008). Collectively, these experiments indicate that, as the mother lays her eggs, she is inserting some form of chemical signal (likely hormonal) into the egg yolk, thus "reaching across" generations to influence a potentially wide range of physiological, morphological and perhaps even behavioral traits of her offspring.

Even if one is uninterested in epigenetics and transgenerational effects on physiology (but how can this topic not fascinate?), the findings of these type of experiments argue for much greater attention on the part of developmental physiologists to the provenance

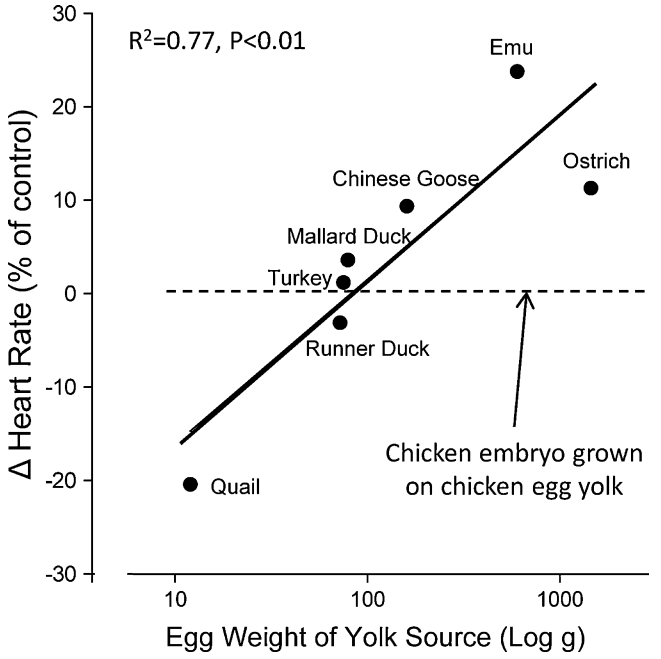

Fig. 5. Epigenetic effects of embryonic environment on heart rate in the chicken embryo. Chicken embryos at 24 h of development were transplanted for further development onto egg yolk from one of 7 species (3 orders) of birds, ranging from an average egg weight of 12 g (Japanese quail) to 1661 g (ostrich). Heart rate of transplanted chicken embryos was then measured at ~3 days of development. The % change in heart rate from control values (chicken embryos grown on their own yolk), was positively correlated with egg mass of the "donor yolk", indicating that yolk environment affects embryo heart rate early in development. (After Ho et al., 2011.)

of our experimental brood stock. Thus, lingering questions remain about many existing studies in developmental physiology that have sought to modify the environment and then look at the consequent responses: "Was that effect in these developing animals the result of the larval environment, or the parental environment"? At the very least, this should argue for more care than we have previously taken in understanding the provenance of the animals we work on. Thus, rather than, for example, being content with getting eggs, larvae, etc. from an animal supplier, paying the bill, and then starting the experiments, we should rather make inquiries of the conditions in which the breeding stock are being kept, how they were transported to the supplier, and perhaps even where *they* came from!

4. Conclusions

Developmental physiology is entering a Golden Age, with interest in how physiology appears, develops and matures at an all-time high (see reviews by Burggren and Warburton, 2005; Pelster et al., 2010; numerous reviews in this volume). In the current article we have highlighted several concepts, further developed some of them, and only hinted at others of importance to developmental physiology in general, and cardio-respiratory physiology specifically. Yet, these various topics should not be viewed as a list of unrelated phenomena, but rather as a network of concepts, influences and – ultimately – effects that can influence our future experiments. Noteworthy is the comment of Gluckman et al. (2009), in writing about epigenetic mechanisms of metabolic and cardiovascular pathologies:

> "During early embryogenesis, the mammalian genome is 'wiped clean' of most epigenetic modifications, which are progressively re-established during embryonic development. Thus, the

epigenome of each mature cellular lineage carries the record of its developmental history. The subsequent trajectory and pattern of development are also responsive to environmental influences, and such plasticity is likely to have an epigenetic basis."

In this single, succinct statement, Gluckman et al. (2009) expose the interconnected nature of developmental plasticity, genetic regulation and epigenetic factors. When we then factor in complex, multi-factor environments and largely unexplored interactions between different organ systems, the true complexity and wonder of how physiology develops begins to be revealed.

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