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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