

Development of physiological regulatory systems: altering the timing of crucial events

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Received July 31, 2002 · Revised version received December 6, 2002 · Accepted December 11, 2002

Summary

There is currently tremendous interest in how the physiology of individual animals changes and develops during ontogeny. One of the key areas is the extent to which the timing and/or rate of physiological development is fixed within an individual and to what extent can it be altered. We propose that plasticity in the timing of the onset of a particular physiological regulatory system *during an individual's development* be referred to as physiological heterokairy (to clearly distinguish this phenomenon from physiological heterochrony, which is an evolutionary pattern), and we marshal evidence for three different patterns of heterokairy: 1. altering relative position in the physiological itinerary; 2. altering overall rate of development *per se* and; 3. a combination of 1 and 2. Using these patterns as a starting point, we develop a framework for investigating physiological heterokairy which takes cognizance of the facts that multiple components of each regulatory system could appear at different times and multiple regulatory systems could come 'on-line' at different times. We finish by placing physiological heterokairy in the wider context of its ecological and evolutionary implications and its relationship to physiological genomics and heterochrony.

Key words: ontogeny, physiological development, heterochrony, physiological genomics

Introduction

The study of animal development has a rich history. Arguably, the basic morphological patterns expressed during ontogeny were more or less catalogued, at least for representatives of the major animal groups, by the beginning of the 20th century (Gilbert, 1985). However, over the last thirty years the explosion in our knowledge of molecular biology, and the application of a more rigorous evolutionary biology to studies in development, have informed and also invigorated classical embryology, evolutionary developmental biology is currently a key area of investigation in the life sciences (Hall, 1999; Holland, 1999; Arthur, 2002).

Notwithstanding the recent 'rediscovery' of developmental biology, our understanding of how physiological regulatory systems appear and change during development (in different animal groups) lags far behind. In

a monograph largely overlooked by contemporary developmental physiologists, Adolph (1968) claimed that "The ontogeny of physiological regulations received no formal study before the twentieth century". His monograph represented a major step in redressing this paucity of data and, perhaps more importantly, provided fellow-workers with a detailed list of key questions signposting how integrated and coherent studies of physiological development should progress.

Despite the explosive growth in interest in the physiological development of a number of different animal groups over the past decade, and the existence of Adolph's (1968) book, a framework within which to investigate patterns of physiological development has not yet been explicitly enunciated. Current work in both vertebrates and invertebrates is largely defined by the physiological system of interest and the species (or group) in which it is studied. We believe that major advances in

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developmental physiology requires cross-disciplinary thinking coupled with experimental manipulation rather than merely adding descriptive studies. A new framework (or frameworks) within which to place past/present work and with which to plan future strategic studies is urgently required if such qualitative advances are to be made (e.g., Burggren and Crossley, 2002). The development of these concepts is particularly timely in that we are now moving into the post-genomic era (Dzau et al., 1999), where future work will concentrate on genomic determination of function (Cowley, 1997; McGovern, 1999). Central to achieving this goal is addressing what is arguably one of the key, unanswered questions (see Adolph, 1968; Burggren, 1999a, b, 2000; Spicer and Gaston, 1999 for others): "Is the timing of the onset of a regulatory system fixed within an individual, or to what extent, if any, can it be altered?" We address this question by proposing some schemes of altered timing of the appearance of physiological regulatory systems at the level of individuals. Where possible, we provide relevant examples to illustrate these schemes. The framework that emerges will be useful in the integration of physiology with development, ecology and evolution.

The problem with heterochrony

Before delving into the question of how the developmental timing of critical physiological events can be modified, we must first deal with a potentially confounding issue – the common use and misuse of the term heterochrony. Few terms in evolutionary biology have been defined so often, so carefully and yet continue to be used so loosely! Strictly speaking, heterochrony is an evolutionary change in the rate and/or timing of developmental processes (Gould, 1977, 1992). While some elements involved in heterochrony (e.g., altering developmental timing) have been legitimately extended from between-species to between-population and even individual development, it is not uncommon to find that the term itself is evoked, leading to confusion and misunderstanding. Numerous attempts to clarify, and even redress, this situation seem to have failed (Gould, 1992; Hall, 1999; McKinney, 1999). The development and status of physiological heterochrony will be discussed elsewhere (Spicer, in prep), and so is not treated in detail here. However, suffice to say that although heterochrony must be related to the *potential* for the alteration in the timing of events during the development of an individual, it is also quite distinct from it. So great care should be exercised to avoid confusing them, a recurrent problem in (morphological) heterochrony studies.

Consequently we propose the terms heterokairy (Gk. *Hetero*, different; *Kairois*, at the right time) to refer to

plasticity in the timing of the onset of developmental events *at the level of an individual during its development*, and physiological heterokairy to refer specifically to plasticity in the timing of the onset of physiological regulatory systems or their components.

Physiological heterokairy

Given the burgeoning of physiological studies looking at developmental changes at the level of individuals (for further discussion see Burggren, 1999a, b, 2000; Spicer and Gaston, 1999) there is urgent need for the study of altered timing of events during the ontogeny of an individual, and exactly how this relates to heterochrony (*evolutionary* change in the rate and/or timing of developmental processes).

A priori approach to alteration of physiological developmental timing

Only a few studies have dealt explicitly with the issue of physiological heterokairy, although it may potentially be a confounding factor in *all* studies of physiological development both between and within species. Nevertheless, several studies provide a reasonable data base to illustrate and to begin an investigation of the phenomenon of heterokairy. We will use these data to illustrate concepts, patterns and principles, with regards to how the appearance of any given physiological regulatory system can be either delayed or brought forward in both real time (i.e., chronological age) and/or in development (i.e., altered rank in a developmental sequence) during an individual's life.

Figure 1 presents a highly stylized representation of different patterns of physiological heterokairy presented in the context of the total chronological time for development of a hypothetical individual (Fig. 1A). Consider a multi-component physiological regulatory system (*r*) that becomes fully functional at a given point in time or onset (O_r) during the development of an individual (Fig. 1B). In Figure 1C, the onset of a functional regulatory system (O_r) is brought forward (n.b., it could equally well be moved back) in an otherwise unaltered developmental program. In Figure 1D, the system is again brought forward (or moved back) but in this case by increasing (or delaying) the rate of overall development *per se*. Here, the rank in a developmental sequence remains unchanged. In Figure 1E, the onset of the system moves as a result of both alterations in the relative timing of onset and in the overall time taken to complete development (in effect a combination of Figs. 1D and 1C).

These simple representations are useful for qualitative comparisons. Theoretically, they may also be employed in a quantitative sense, although there are difficulties in

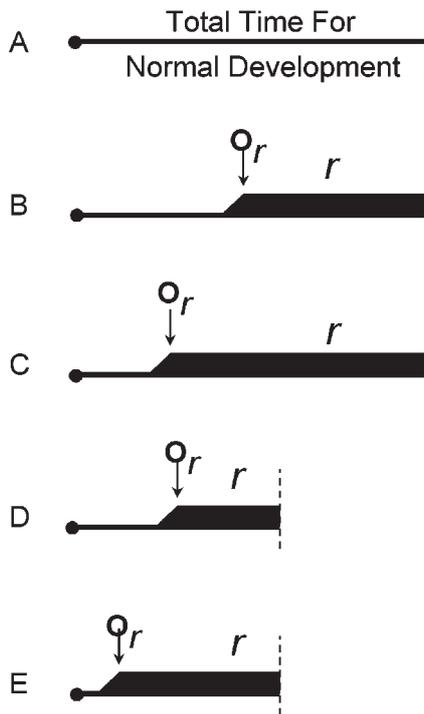


Fig. 1. The onset of physiological regulation can change during development. Consider the chronological time for complete development from fertilized egg to adult (A). (B) depicts a regulatory system, r , with a time of onset, O_r during development. O_r can appear earlier in development, and in chronological time, by altering its rank in the sequence of other developmental events (C). Alternatively, O_r can be moved forward in chronological time if the total time for development (developmental time) is shortened (D). Finally, O_r can be moved forward by altering both the timing of its appearance relative to other developmental events and by reducing the chronological time required for development (E).

application (see below). Having described these patterns we now marshal evidence, taken from actual studies, for the extent to which each of them is both possible and prevalent.

Moving the onset of a functional regulatory system within a largely unaltered-developmental program

Implicit in this pattern (Fig. 1C and therefore, it follows in Fig. 1E also) is the important question: To what extent is it possible to uncouple the appearance and development of a physiological regulatory system from overall morphological development and still end up with a viable individual? Considerable data illustrating this pattern are presented and discussed by Spicer and Gaston (1999), and includes alterations in the ontogeny of respiratory regulation in crustaceans by culture under environmental hypoxia and the onset of thermoregulation in oilbirds. Seawater tolerance and associated

physiological changes in the gills of freshwater salmonids can be brought forward by hormonal treatment (cortisol, growth hormone, and insulin-like growth factor; McCormick et al., 1991, McCormick, 1994). We conclude that moving the appearance of a functional regulatory system within a largely unaltered developmental program is both possible and a prevalent feature of many developmental itineraries.

Moving the onset of a functioning regulatory system by altering the chronological time taken for an animal to accomplish its developmental itinerary

Any stimulus that alters the chronological time required to reach a defined point in development, e.g., birth/hatching, metamorphosis, sexual maturity, death, must also alter the timing of the appearance of physiological regulation regulatory systems, assuming that the relative timing of the appearance (e.g., half way through programmed development) remains the same (Fig. 1D). For example, enhanced development and metamorphosis occurs in a variety of amphibian larvae when thyroxin, growth hormone, or their analogues are administered (for an extensive literature see Burggren and Just, 1992). Thus, the numerous physiological systems that develop will come on-line earlier in chronological time. As another example, eggs of the brackish-water amphipod *Gammarus duebeni* hatch after 21 days compared with 17 days when salinity is increased from 10 to 20 PSU (Morritt and Spicer, 1996). In each of the above examples, the chronological time to complete development is sharply altered, but the relative appearance in ontogeny of many of the physiological regulatory systems seems to be held constant.

One of the simplest and most common ways of seemingly causing a simple alteration in absolute time for development in ectotherms is to alter their environmental temperature. This assumption is embodied in numerous attempts made to compare growth in ectotherms independently of temperature, such as the calculation of day-degrees (e.g., Pritchard et al., 1996; Weltzien et al., 1999). While temperature has been used as a convenient tool to accelerate and decelerate developmental itineraries, in reality its numerous, interrelated effects can be very difficult to unravel (see below).

Moving the onset of a functional regulatory system by altering both the onset of regulation and the length of the developmental program

Figure 1E depicts a situation where the duration of the developmental program is altered and the timing of the onset of a functioning regulatory system is altered within that program. While this likely describes a situation that may be most prevalent in developing individuals, there is a paucity of experimental data supporting it. One ex-

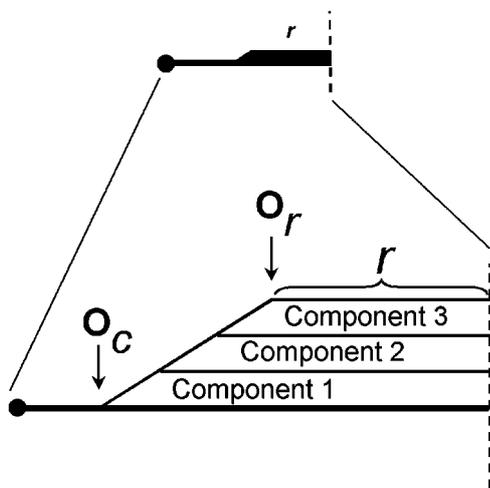


Fig. 2. A regulatory system, r , is typically composed of numerous components. In this figure depicting a 3-component system, O_c is marked by the onset of component 1, but the onset of regulation, O_r , does not occur until the third and final component is in place.

ample where both the duration of the developmental program and the timing of the onset of a functioning regulatory system are both altered is the ability of brine shrimp to maintain oxygen uptake during hypoxia (Spicer and El-Gamal, 1999). The 'adult' pattern of respiratory regulation co-occurs with segmentation when brine shrimp are cultured in air-saturated sea water. Overall development is accelerated during chronic hypoxia, leading to an earlier onset of respiratory regulation in chronological time, but the actual the pattern of regulation now appears before segmentation, i.e., earlier in the developmental itinerary. Thus the onset of respiratory regulation occurs earlier in both chronological time and the sequence in which it appears.

The investigation of physiological heterokairy

While the patterns described above provide a useful starting point in the framework of heterokairy, they are too simplistic to have much real operational value. Having described different scenarios for what *could* happen to alter the timing of the appearance of any one physiological regulatory system, we now need to take cognizance of the fact that in an animal's lifetime numerous physiological systems are required to come on line, and not all at the same time. Furthermore, no regulatory system suddenly appears fully functional or in isolation. Rather, it is normally the result of a slow, deliberate construction from an assemblage of constituent parts. The complexity of physiological regulation in an individual reflects the fact that regulatory systems do function in an integrated fashion, even if we do not often study them in this way. Any scheme which does not attempt to take each and all of these features into

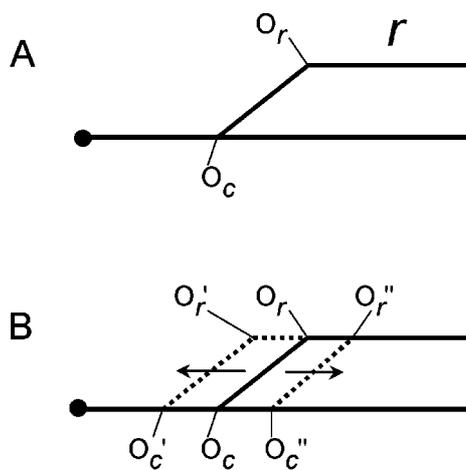


Fig. 3. The onset of physiological regulation, O_r , is preceded by the onset of the components O_c , that ultimately come together to form the regulatory system (A). O_c can be moved forward or backward in development, thus shifting the onset of regulation, O_r (B).

account will be limited in its conceptual and operational value. Consequently, we now present a scheme that incorporates firstly, multiple components to each regulatory system potentially appearing at different times, secondly, multiple regulatory systems potentially coming on line at different times, and thirdly, the integration of these systems once they are in operation. So far, we have referred to the onset of a fully functioning physiological regulatory system as a single point in time, O_r (Fig. 1). In reality, all the components of the system must be assembled before the regulatory system becomes fully functional. Each regulatory system is composed of numerous components and each component may become competent at a different time during the ontogeny of the regulation. The appearance of the first of many components of the regulatory system is represented as the onset of components (O_c) in Figures 2 and 3A. Note that such a scheme assumes that all components must necessarily be in place before the appearance of a fully-functional regulatory system. To visualise how this scheme could be applied, consider the major components of a simple reflex arc, a sensor, an integrator, and an effector (examples of components of that regulatory system). While any one of these three components could be the first to appear, all three must be present for the reflex arc to function. In theory, there are numerous different ways to modify the appearance of the components of any given regulatory systems, thereby affecting the timing of the onset of a fully formed regulatory system (O_r). All of these, collectively or in part, comprise what we here refer to as physiological heterokairy.

Based on this view of a regulatory system's development, changing O_r becomes a more complex process than was evident from the simple schematic employed

above. Here, changes in O_r involve changes in timing of one or more of the constituent components, and are related in a number of different ways to changes in O_c (Figs. 3B and 4). Let us now consider the different ways O_r and O_c may (or may not) change relative to one another. In Figure 3B, the relative timing of the components indicated in Figure 2 remains fixed, but O_c occurs either earlier (O_c') or later (O_c''). These changes in O_r thus occur strictly because of changes in O_c with no change in relative timing in appearance of the various components of the regulatory system. If we return to the example of the reflex arc, the sensor, integrator, and effector all appear earlier by the same amount of time, shifting the onset of the reflex. Figure 4A shows a variant theme, in which the appearance of first constituent (O_c) is fixed but the timing of the onset of the physiological regulatory system (O_r) changes because the time of the appearance of the last necessary components is either brought forward (O_r') or delayed (O_r'') during development. In terms of the reflex arc, the first constituent still appears at the same time, but the onset of the reflex now occurs at a different time. The onset of the functioning system is determined by the timing of the appearance of the final, necessary constituent, which in turn may be determined or influenced by the timing of the appearance of the constituent(s) that come before it.

Another developmental option is for the appearance of the constituents O_c to differ (O_c' , O_c''), but for O_r , to remain unchanged (Fig. 4B). That is, the onset of the reflex is unchanged despite the first component being brought forward or delayed in time. Yet again the onset of the functioning system is determined by the timing of the appearance of the final necessary constituent. Figure 4C combines what we have already considered separately in Figure 4A and Figure 4B, presenting the different scenarios resulting from changes in timing of both the appearance of the constituents (O_c' and O_c'') and the onset of a functioning regulation system (O_r' , O_r'').

Our model presumes that all components must necessarily be in place before the onset of functioning regulatory system. However, there is potentially more than one way of achieving a given alteration in onset timing. For example, consider the regulation of oxygen uptake in the face of declining environmental oxygen tensions. This regulation is achieved through a number of different physiological mechanisms, singly and in combination, including increases in ventilation, perfusion, the carrying capacity and oxygen affinity of blood/hemolymph, metabolic enzymes, etc. (Lutz and Storey, 1997). The changes in the developmental pattern of the regulatory system may thus be achieved not by depending upon changes in the timing of all original components, but rather by recourse to 'new' or 'additional' components. In *Artemia*, for example, the appearance of an 'adult' pattern of respiratory regulation (i.e., the marked ability to maintain oxygen uptake in

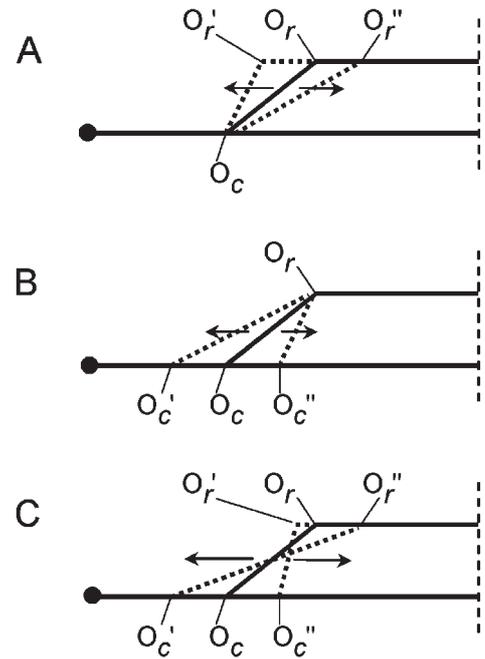


Fig. 4. The timing of O_c and O_r is not fixed. In (A), O_c remains unchanged in development, but O_r can be moved forward to O_r' or backward to O_r'' . Alternatively, O_r can remain fixed, while O_c is moved forward to O_c' or backward to O_c'' (B). Most complex of all, both O_c and O_r can move relative to one another in numerous ways (C).

the face of acutely declining oxygen tensions) in individuals reared under normoxic conditions co-occurs with the formation of functional gills and heart (Spicer and El-Gamal, 1999). However, when cultured under hypoxic conditions this regulation appears earlier both in chronological time and in development (i.e., before the heart and gills have formed). The early appearance of the 'adult' pattern in chronically hypoxic animals is achieved *via* an alternative physiological mechanism, in this case increasing the hemoglobin concentration of the blood early in development. Thus, the possibility of patterns of regulation being achieved by different means, under different environmental conditions, should be kept in mind when testing our model. Whether altering the timing of the appearance of a regulatory system or altering the identity of the components of regulation is most common, is one of the key questions emerging from the framework of physiological heterokairy.

The framework for the study of physiological development described above provides a detailed way of explaining how physiological regulatory systems change during development. Relevant experimental data drawn in pieces from a variety of studies suggest that at least components of it are valid, though the verification of this model must await the outcome of studies that actually use it as a framework for experimental design.

Physiological heterokairy: an integrative approach

The framework presented indicates how the onset of a single regulation might be modified during development. Of course, the successful development of an individual requires that a multitude of different but often inter-related regulatory systems develop, and often at different times in an individual's development. In mammals, for example, regulated blood flow occurs before regulated lung ventilation and regulated renal function, which in turn occur before regulation of body temperature. To take a specific invertebrate example, in brine shrimp osmoregulation is established just before hatching, while cardiovascular regulation and respiratory regulation co-occur and are post-hatch events. Figure 5 illustrates a hypothetical situation where, intrinsic and/or extrinsic factors effect changes in the order of

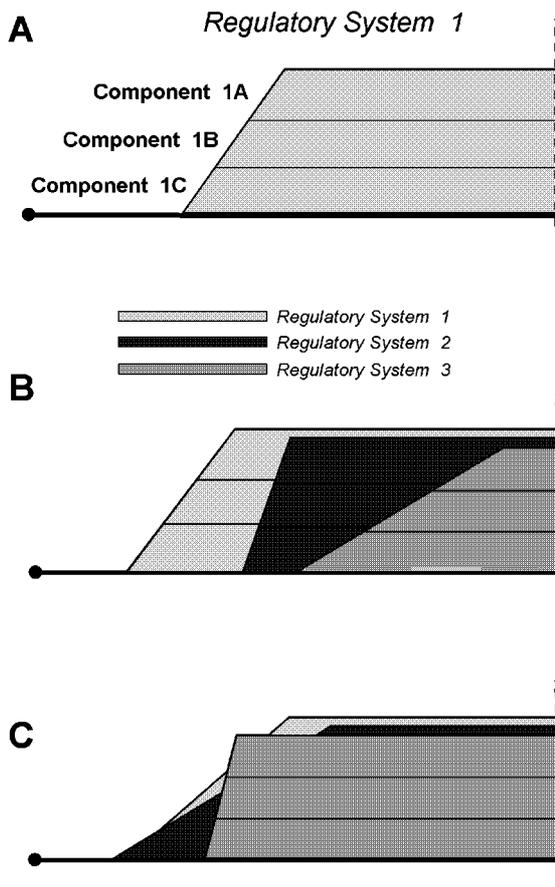


Fig. 5. Overall physiological regulation is the result of numerous regulatory system. (A) shows the development of a single three component regulatory system. In (B), the development of three multi-component systems are shown, each with their own distinctive O_c and O_r . (C) shows how the O_c and O_r for each system can themselves appear at different points in development, altering both the rate and absolute timing of the appearance of each system.

appearance of an animal's regulatory systems. An example of this is that when brine shrimp are reared under hypoxia respiratory regulation appears before cardiovascular regulation instead of them co-occurring as mentioned above. Despite previous developmental events, there are likely to be developmental constraints on the extent to which the appearance of different organ systems can be varied because of their potential co-dependence. For example, physiological functions that depend upon convective transport by blood must await circulatory development, but the circulation can move forward without necessary advancement of all convection-dependent systems. Similarly, the nervous system could develop in advance of the skeleto-muscular system, but without muscles to stimulate, arguably little is achieved.

Taking our discussion to its logical conclusion, we see that just as the physiological sum of an individual is actually the integrated responses of multiple systems, so each system is actually the sum of sub-components, through organs, tissues, cells, and even down to gene-molecular level (Fig. 6). Moreover, each of the conceptualised changes we have described (e.g., shifts in O_r and O_c , recruitment of new components or systems at the level of the regulatory system r) can occur simultaneously at different levels in this physiological regulatory hierarchy. While the complexity of the resultant system(s) can quickly appear overwhelming, it nonetheless can be reduced to manageable pieces and used to formulate testable hypotheses. In the same way that the composite model of the mammalian circulation,

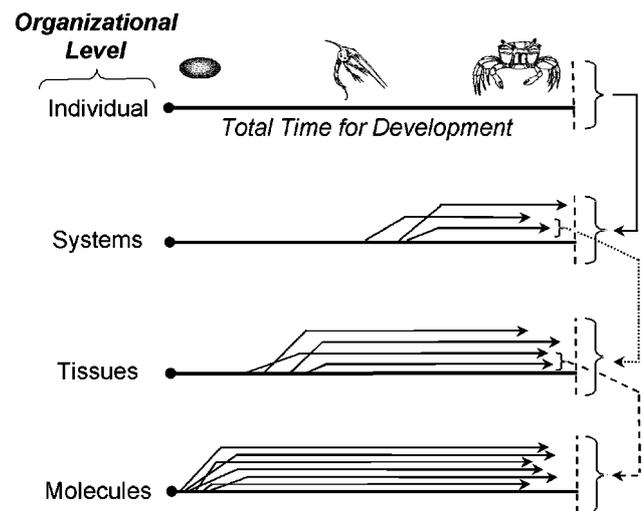


Fig. 6. Physiological regulation can be viewed at numerous functional levels, from the individual down to its constituent molecules. At each organizational level, nested under the next highest level, the onset of multiple components during development can be similarly modeled.

developed over decades, is enormously complex and at first glance quite bewildering (see Guyton and Coleman, 1969), it nonetheless was developed piece by piece, and can readily be broken down into its components parts for additional study.

Future opportunities and new directions

Investigating physiological heterokairy

We do not claim that our scheme will be broad enough to embrace all eventualities in the future study of developmental physiology and neither do we believe it is the only one possible. However, it does provide a framework in which to place future studies, and perhaps more importantly, allow investigators to be strategic in identifying key questions and planning appropriate investigations in the developmental physiology of an individual. Even if this paper merely stimulates informed discussion and/or promotes the development of a stronger conceptual base for developmental physiology, it will have served some purpose.

The relationship between heterokairy and heterochrony

Although rarely referred to explicitly as physiological heterochrony, there are many cases of interspecific differences in the timing of physiological events during development within individuals. The development of thermoregulation in altricial and precocial birds and mammals (Vleck et al., 1979; Bucher, 1986; Webb and McClure, 1989) and differences in salinity tolerance between different salmonid species (McCormick, 1994) are just two well-known examples. Having suggested and defined the term *physiological heterokairy* our next task must be to point out that heterokairy should not be confused with heterochrony. However, to do this we must know the extent to which purported between-species differences in timing can be explained by heterokairy. We are not suggesting that all investigators interested in genetically-fixed differences in the timing of physiological events are in fact examining the developmental plasticity of an individual, though this is not impossible (see Spicer and Gaston, 1999). But it is of primary importance that we know exactly how physiological heterokairy relates to physiological heterochrony, and to what extent can heterochrony be explained, or accounted for, by heterokairy. Fortunately there is fast becoming available a set of analytical tools that will allow us to investigate sequence changes in both physiological heterokairy and heterochrony (e.g., Smith 2001, 2002; Jeffrey et al., 2002a, b). The problem we have at present is we do not yet have the amount and type of data which is required to employ these techniques although, thankfully, this is changing.

Temperature – a special case?

In the context of our framework, the onset of physiological regulation in chronological time can be induced earlier, for example, by an increase in temperature (i.e., moving from B to D in Fig. 1). However, we raise the question of whether temperature is a “special case”. For example, growing fish at increasingly higher environmental temperatures not only results in the early appearance of functional muscles, but also qualitatively alters the biochemical constituents of those muscles and hence their functional properties (e.g., Johnson et al., 1996; Temple et al., 2001). Another example is the effect of temperature on certain crocodylian and chelonian reptile embryos, where a swing of a few degrees in incubation temperature not only alters the total time required for development to hatching, but also alters gender and presumably the myriad of associated physiological regulations (Bull, 1980; Gutzke and Crews, 1988).

Given these complexities, does a temperature-induced acceleration in the chronological time required for onset of a physiological regulation comprise physiological heterokairy as indicated in Figure 1D? From a strictly ecological perspective, *any* stimulus that hastens development in chronological time and accelerates the transition to the adult animal will have potential fitness effects by reducing the time spent in each developmental stage. A reduction in the chronological time required for development likewise may reduce the risk of predation at each stage, and reduce the chronological time required for reaching sexual reproduction. Thus, from an ecological perspective, the key point is that the arrival of the adult, sexually mature species has been accelerated, and only secondary is the specific nature of the driving stimulus (temperature in this case). From this perspective, temperature would be viewed as just another agent of change along with hypoxia, food availability, crowding, and numerous other environmental factors known to have (or suspected to have) specific effects on animal development.

Methodology

One potential problem encountered in studying physiological heterokairy is that the physiological measurements of interest currently require at worst the ultimate destruction of the individual being studied and at best reliance on invasive techniques which may themselves alter the outcome of subsequent measurements (Spicer and Gaston, 1999). Consequently one of the great challenges (and opportunities) for developmental physiology is the continued development and refinement of non-invasive techniques and technologies (Burggren, 1987). Unfortunately, non-invasive techniques are limited to particular types of physiological measurement

and almost by necessity we will have to continue to employ between-individual studies (of individuals at different stages of development) to infer within-individual changes in physiology. However, it should always be kept in mind that by employing different individuals in studies of physiological development we run the risk of obscuring, or even swamping, developmental changes if the between-individual variation we encounter is as great, or even greater than the within individual variation we are interested in.

Physiological heterokairy and physiological genomics

The chief proponents of functional genomics claim that this field will lead to a renaissance and rethinking of physiology (Cowley, 1997; Dzau et al., 1999; Strausberg and Austin, 1999; McGovern, 1999). Aristotle contended that things are best studied as they come into being. Taking both thoughts in concert, then, physiological heterokairy (and the development of physiological function generally) should be regarded as a key area in physiological genomics. Linking genomic sequencing and mapping to understanding the development of the integrative physiology of an individual is an exciting prospect, *although it will not answer all of our ecological and evolutionary questions*. To some extent the work linking developmental genetics to developmental physiology has started (e.g., Kopp and Klotman, 1995) but it is true to say that what we currently see is only the beginning. Most of the emphasis of functional genomics will of course be on human health. Moreover, we are restricted in the number of animal models for which we have genomic data as well as the unduly narrow range of models currently under favor (see Burggren, 2000). Yet, these limitations should not preclude investigation using a functional genomic approach to some of the central tenets of developmental physiology.

Ecological and evolutionary implications

Although a discussion of the many ecological and evolutionary implications of physiological heterokairy is beyond the scope of this paper, these implications are important and deserve future attention. Central to future discussion must be the relationship (if any) between physiological heterokairy and Darwinian fitness. For example, early appearance of a regulatory process (teamed with development of an organ/tissue) might increase the likelihood of survival, which is one of the key components of fitness in the Euler-Lotka equation (Sibly and Calow, 1987). Development of a tissue or organ might result in the early appearance of sexual maturity and/or reproductive output, and of course time to first reproduction is also a key component in fitness. Such altered development could be selected for, at the

expense of other systems/organs/tissues, if fitness ultimately was increased.

Alternatively or in addition, altered physiological development could occur at the expense of other fitness components (e.g., growth or total reproductive output). This occurs in brine shrimp where accelerating the onset of respiratory regulation early in development is correlated with a decrease in fitness (as measured by total reproductive output; Spicer and El-Gamal, 1999). It also occurs in polychaetes, bryozoans and crustaceans, where delayed metamorphosis results in a decrease in fitness (e.g., Gebauer et al., 1999). An individual might also delay the development of an energetically expensive system, to feed the normal development of systems potentially "starved" by environment. An example is found in the cycles of atrophy and regeneration of snake digestive system in response to food availability (Secor and Diamond, 1998). Clearly integrating physiological heterokairy and Darwinian fitness is an important research priority.

Epilogue

The explosion of developmental physiological studies, particularly using a comparative approach, is producing an ever increasing body of data on how animal function develops, and how that development is affected by genes and environment. Comparative physiology is increasingly driven by a desire to recognize patterns within data and provide increasingly complex conceptual frameworks that draw upon evolutionary biology, ecology, developmental biology and molecular biology (see Garland and Carter, 1994; Bennett, 1997; Weibel et al., 1998; Spicer and Gaston, 1999; Feder et al. 2000; Burggren and Crossley, 2002). As the discipline of developmental physiology undergoes rapid growth, it behooves developmental physiologists to likewise develop testable hypotheses and propose ever more sophisticated conceptual foundations, even if this means becoming multidisciplinary, leaving our comfort zone for the sake of chasing the best and most interesting questions. We must continue to debate the key concepts and to work towards a unified understanding of the theoretical underpinnings of our own, and other disciplines, that will allow us to address the key questions in developmental physiology.

References

- Adolph, E. F. 1968. *Origins of Physiological Regulations*. Academic Press. New York.
- Arthur, W. 2002. The emerging conceptual framework of evolutionary developmental biology. *Nature* 415: 757–764.

- Bennett, A. F. 1997. Adaptation and the evolution of physiological characters. In: *Handbook of Physiology, Section 13: Comparative physiology, Vol. 1* (W.H. Dantzler ed.). Oxford University Press, New York, pp. 3–10.
- Bucher, T. L. 1986. Ratios of hatchling and adult mass-independent metabolism: A physiological index to the altricial-precocial continuum. *Resp. Physiol.* 65: 69–84.
- Bull, J. J. 1980. Sex determination in reptiles. *Q. Rev. Biol.* 55: 4–21.
- Burggren, W. W. 1987. Invasive and noninvasive methodologies in ecological physiology: a plea for integration In: *New Directions in Ecological Physiology* (M. E. Feder, A. F. Bennett, W. W. Burggren and R.B. Huey eds.). Cambridge University Press, Cambridge, pp. 251–274.
- Burggren, W. W. 1999a. Studying physiological development: Past, present and future. *Biol. Bull. NTNU* 33: 71–84.
- Burggren, W. W. 1999b. Genetic, environmental and maternal influences on embryonic cardiac rhythms. *Comp. Biochem. Physiol.* 124A: 423–427.
- Burggren, W. W. 2000. Developmental physiology, animal models, and the August Krogh principle. *Zoology-Analysis of Complex Systems* 102: 148–156.
- Burggren, W. W. and D. A. Crossley II. 2002. Comparative cardiovascular development: improving the conceptual framework. *Comp. Biochem. Physiol.* 132A: 661–674.
- Burggren, W. W. and J. J. Just. 1992. Developmental changes in physiological systems. In: *Environmental Physiology of the Amphibians* (M. E. Feder and W. W. Burggren eds.). University of Chicago Press, Chicago, pp. 467–530.
- Cowley, A. W. Jr. 1997. Genomics to physiology and beyond: How do we get there? *The Physiologist* 40: 205–211.
- Dzau, V. J., M. J. F. Austin, P. Brown, C. A. Housman, R. Mulligan and R. Rosenberg. 1999. Revolution and renaissance. *Physiol. Genomics* 1: 1–2.
- Feder, M. E., A. F. Bennett and R. Huey. 2000. Evolutionary physiology. *Annu. Rev. Ecol. Syst.* 31: 315–341.
- Garland, T. Jr. and P. A. Carter. 1994. Evolutionary physiology. *Annu. Rev. Physiol.* 56: 579–621.
- Gebauer, P., K. Paschke and K. Anger. 1999. Costs of delayed metamorphosis: reduced growth and survival in early juveniles of an estuarine grapsid crab, *Chasmagnathus granulata*. *J. exp. mar. Biol. Ecol.* 238: 271–281.
- Gilbert, S. F. (ed.). 1985. *A Conceptual History of Modern Embryology*. Plenum Press, New York.
- Gould, S. J. 1992. Heterochrony. In: *Keywords in Evolutionary Biology*. (E. Fox and E. Lloyd eds.). Harvard University Press, Cambridge, Mass., pp. 158–167.
- Gould, S. J. 1997. *Ontogeny and Phylogeny*. Harvard University Press, Cambridge, Mass.
- Guyton, A. C. and T. G. Coleman. 1969. Quantitative analysis of the pathophysiology of hypertension. *Circ. Res.* 24: (Suppl. 1), 11–119.
- Gutzke, W. H. N. and D. Crews. 1988. Embryonic temperature determines adult sexuality in a reptile. *Nature* 332: 832–834.
- Hall, B. K. 1999. *Evolutionary Developmental Biology*. Chapman and Hall, London.
- Holland, P. W. H. 1999. The future of evolutionary developmental biology. *Nature* 402: c41–c44.
- Jeffrey, J. E., M. K. Richardson, M. L. Coates and O. R. P. Bininda-Emonds. 2002. Analyzing developmental sequences within a phylogenetic framework. *Syst. Biol.* 51: 478–491.
- Jeffrey, J. E., O. R. P. Bininda-Emonds, M. L. Coates and M. K. Richardson. 2002. Analyzing evolutionary patterns in vertebrate embryonic development. *Evol. Dev.* 4: 292–302.
- Johnston, I. A., V. L. A. Viera and J. Hill. 1996. Temperature and ontogeny in ectotherms: muscle phenotype in fish. In: *Phenotypic and Evolutionary Adaptations of Organisms to Temperature* (I. A. Johnston and A. F. Bennett eds.). Cambridge University Press, Cambridge, pp. 153–181.
- Kopp, J. B. and P. E. Klotman. 1995. Transgenic animal models of renal development and pathogenesis. *Am. J. Physiol.* 269: F601–F620.
- Lutz, P. L. and K. B. Storey. 1997. Adaptations to variations in oxygen tension by vertebrates and invertebrates. In: *Handbook of Physiology, Section 13: Comparative Physiology, Vol. 2* (W.H. Dantzler, ed.). Oxford University Press, New York, pp. 1479–1522.
- McCormick, S. D. 1994. Ontogeny and evolution of salinity tolerance in anadromous salmonids: Hormones and heterochrony. *Estuaries* 17: 26–33.
- McCormick, S. D., W. W. Dickhoff, J. Duston, R. S. Nishioka and H. A. Bern. 1991. Developmental differences in the responsiveness of gill sodium, potassium ATPase to cortisol in salmonids. *Gen. Comp. Endocrin.* 84: 308–317.
- McGovern, V. 1999. Exploring the topography of physiological genomics. *Physiol. Genomics* 1: 21–23.
- Morritt, D. and J. I. Spicer. 1996. The culture of eggs and embryos of amphipod crustaceans: Implications for brood pouch physiology. *J. Mar. Biol. Ass. UK* 76: 361–376.
- Pritchard, G., L. D. Harder and R. A. Mutch. 1996. Development of aquatic insect eggs in relation to temperature and strategies for dealing with different thermal environments. *Biol. J. Linn. Soc.* 58: 221–244.
- Secor, S. M. and J. Diamond. 1998. A vertebrate model of extreme physiological variation. *Nature* 395: 659–662.
- Sibley, R. M. P. and Calow. 1987. *Physiological Ecology of Animals: An Evolutionary Approach*. Blackwells Scientific, Oxford.
- Smith, K. K. 2001. Heterochrony revisited: the evolution of developmental sequences. *Biol. J. Linn. Soc.* 73: 169–186.
- Smith, K. K. 2002. Sequence heterochrony and the evolution of development. *J. Morphol.* 252: 82–97.
- Spicer, J. I. and M. M. El-Gamal. 1999. Hypoxia accelerates the development of respiratory regulation in brine shrimp – but at a cost. *J. exp. Biol.* 202: 3637–3646.
- Spicer, J. I. and K. J. Gaston. 1999. *Physiological Diversity and its Ecological Implications*. Blackwells Science, Oxford.
- Strausberg, R. L. and M. F. J. Austin. 1999. Functional genomics: technological challenges and opportunities. *Physiol. Genomics* 1: 25–32.
- Tazawa, H., W. Watanabe and W. W. Burggren. 1994. Embryonic heart rate in altricial birds, the pigeon (*Columba domestica*) and the bank swallow (*Riparia riparia*). *Physiol. Zool.* 67: 1448–1460.
- Temple, G. K., N. J. Cole and I. A. Johnston. 2001. Embryonic temperature and the relative timing of muscle-specific genes during development in herring (*Clupea harengus* L.). *J. Exp. Biol.* 204: 3629–3637.
- Vleck, C. M., D. F. Hoyt and D. Vleck. 1979. Metabolism of avian embryos: patterns in altricial and precocial birds. *Physiol. Zool.* 52: 363–377.
- Webb, D. R. and P. A. McClure. 1989. Development of heat production in altricial and precocial rodents: Implications for the energy allocation hypothesis. *Physiol. Zool.* 62: 1293–1315.
- Weibel, E. R., C. R. Taylor and L. C. Bolis. 1998. *Principles of Animal Design. The Optimisation and Symmorphosis Debate*. Cambridge University Press, Cambridge.
- Weltzien, F. A., M. Planas and H. J. Fyhn. 1999. Temperature dependency of early growth of turbot (*Scophthalmus maximus* L.) and its implications for developmental progress. *J. exp. mar. Biol. Ecol.* 242: 201–210.