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Development Strategies and Biodiversity

Darwinian Fitness and Evolution in the Anthropocene

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Editors
David Costantini
Muséum National d'Histoire Naturelle
Paris, France

Valeria Marasco
Konrad Lorenz Institute of Ethology
University of Veterinary Medicine Vienna
Vienna, Austria

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D.C. dedicates this book to the memory of his father
V.M. dedicates this book to her family, especially her daughter Diana

Preface

From plant to animal species, development is a complex and dynamic process involving the cross talk among genes, maternal effects, epigenetic mechanisms, and environmental circumstances. Such interactions shape the individual's life history trajectories, influencing key traits like growth, reproduction, and senescence. These effects are not limited to a single generation, but can also be passed on future generations in what we call transgenerational effects. This book will illustrate how and why early life experience shapes biodiversity and how this diversity translates into different Darwinian fitness outcomes. To this end, we have recruited scientists with different backgrounds and research interests, and spanning different taxa. The resultant chapters represent a rich series of topics related to developmental plasticity and early life experience, with emergent and interconnected themes. The book kicks off focusing on the evolutionary meaning of developmental strategies, and on how and why early life experience generates diversity. In Chap. 1, "*More than fifty shades of epigenetics for the study of early in life effects in medicine, ecology and evolution*," Danchin (i) points out the central role of epigenetics, as a transgenerational form of biological memory, in driving the early life effects and their consequences in eco-evolutionary dynamics, and (ii) proposes an inclusive understanding of epigenetics (inclusive evolutionary synthesis), incorporating all the processes of parent–offspring resemblance that are not engraved into the DNA sequence. Staying on the subject of transgenerational inheritance, in Chap. 2, "*For better or worse: benefits and costs of transgenerational plasticity and the transhormesis hypothesis*," Costantini proposes the transhormesis hypothesis, whereby the molecular memory generated by hormetic priming of the parents to low-moderate doses of environmental stressors during sensitive windows of life is being transmitted to their offspring, so that they are better prepared to withstand anthropogenic challenges. In Chap. 3, "*Adaptive meaning of early life experience in species that go through metamorphosis*," Koyama et al. focus on the adaptive meaning of one particular widespread mode of development called metamorphosis. They review (i) the ways in which various insect species adjust the timing of metamorphosis and the morphogenetic processes during metamorphosis depending on their environment during the

juvenile stage and discuss (ii) the adaptive significance and the endocrine basis of these plastic responses. The second theme of the book is dedicated to address some of the most relevant endogenous molecular mechanisms linking the consequences of early life environmental conditions and adult performance. In Chap. 4, "*Early-life stress drives the molecular mechanisms shaping the adult phenotype*," Huber et al. provide an overview of studies on the long-lasting effects of exposure to early life stress on the adult phenotype. They focus on the actions of elevated developmental glucocorticoid hormones in shaping adult physiological stress responses and in organizing key cellular and molecular mechanisms underlying the evolution of life histories, including oxidative stress, telomere dynamics, and epigenetic processes. The authors draw particular attention to the accumulating recent evidence showing that exposure to certain early life stressors can promote adaptive coping mechanisms of stress resilience to later life challenges, thus potentially ameliorating fitness outcomes. They finally emphasize the need of future research to determine the key features acting as relevant modulators of the biological embedding of early life stress leading to a distant memory in stress vulnerability *vs* resilience. In Chap. 5, "*Environmental conditions in early life, host defenses and disease in late life*," Sorci and Faivre provide an overview of the possible environmental features experienced in early life that can affect immunological defense strategies and the appearance of a disease at late age. In particular, they draw a parallel between the developmental origin of health and disease hypothesis and what they call the immune origin of health and disease hypothesis. In so doing, they postulate that early environmentally driven shaping of the immune system sets a program that might account for future susceptibility to infection and immune-mediated diseases, ultimately affecting organismal fitness. In Chap. 6, "*Early life nutrition and the programming of the phenotype*," Buchanan et al. have highlighted the multitude of ways in which early life diet can impact on development, with consequences for adult phenotype and ultimately fitness. They also highlight that we know a vast amount about how diet impacts development, but that such knowledge is limited to a few study organisms. Thus, any inferences rarely allow for interpretation of the adaptive significance of such diet effects in mediating developmental trade-offs or the impacts on fitness in wild animals. In the third and final theme of the book, relying on examples of how early life stressors affect the way organisms respond to the ongoing and future environmental challenges of the Anthropocene, this book takes a novel approach to specifically address the adaptive meaning of early life experience. The new challenges for wildlife created by humans provide a natural laboratory to study in real time the interplay of a myriad of processes both of natural and human-driven origin. In Chap. 7, "*Adaptive and maladaptive consequences of larval stressors for metamorphic and postmetamorphic traits and fitness*," Stoks et al. also focus on taxa that go through metamorphosis, but addressing how stressors encountered in the larval stage affect phenotypic development, and eventually carry over across metamorphosis and shape the adult fitness. They also (i) show that stress exposure of larvae may also change tolerance to stressors encountered in the adult stage and (ii) illustrate the largely unexplored effects of larval stressors on the (post-) metamorphic body composition, which may have the potential to scale up and change

biotic interactions and nutrient fluxes across ecosystems. In Chap. 8, "*Plastic aliens: developmental plasticity and the spread of invasive species*," Cordeschi et al. explore the relevance of biological invasions in the Anthropocene. They tackle this topic making the point that developmental plasticity can shape the ideal invader. Developmental plasticity is predicted to promote the capacity of species to invade novel habitats, by favoring the optimal match between individual phenotypes and the new environment, during the early steps of an invasion. In addition, Cordeschi et al. point out that the study of biological invasions has also great potential to provide an excellent natural laboratory to investigate the adaptive meaning of development strategies, early life experience, and predictive power of environmental (mis)-matching models. Finally, in Chap. 9, "*Consequences of developmental exposure to pollution: importance of stress-coping mechanisms*," Angelier focuses on the impact of pollutants on biodiversity, highlighting how developmental exposure to a chemical or physical pollutant may disrupt stress-coping mechanisms with detrimental consequences later in life. Angelier also emphasizes (i) the need for more research on the cumulative and interactive effects of physical and chemical pollutants on stress-coping mechanisms and performance, (ii) the relevance of early life hormesis in adjusting the functioning and the flexibility of stress-coping mechanisms to a polluted environment, and (iii) the need to assess whether selection acts on stress-coping mechanisms and favors specific stress-coping traits that are beneficial in a polluted world. Although the book is not exhaustive, by relying on specific examples, we have attempted to tackle a holistic and multidisciplinary approach, from the evolution of tempo and mode of development, the molecular mechanisms fine-tuning developmental trajectories, to the (mal)adaptive consequences of developmental plasticity for organisms facing the emerging, fast-growing challenges of the Anthropocene. As never before, we urgently need to pave the way for addressing the challenges that Anthropogenic changes pose to biodiversity on Earth. Probably one of the most relevant take-home messages of this book is that we need to centralize research efforts in integrating concepts and theory of developmental plasticity with environmental sciences at the individual, population, and community levels with the goal to predict whether plasticity will favor adaptation to the Anthropogenic world. It is our hope that readers will find these chapters interesting and stimulating new frontiers of research. We are heartily grateful to the authors of the various chapters for committing to the writing of this book especially in light of the current challenging times due to the global pandemic of coronavirus disease 2019, and for sharing their expertise and experiences.

Paris, France — David Costantini
Vienna, Austria — Valeria Marasco

Contents

Part I
Evolutionary Meaning of Development: How and Why Early Life Experience Generate Diversity

Chapter 1
More than Fifty Shades of Epigenetics for the Study of Early in Life Effects in Medicine, Ecology, and Evolution

Etienne Danchin

Abstract After being coined by Conrad Waddington in the context of development, today the term epigenetics focuses on the molecular machinery beyond genes. Epigenetics is central to early in life effects and their consequences in eco-evolutionary dynamics. I review the two historical understandings of epigenetics, i.e. its Developmental and Evolutionary understandings, both concerning the molecular mechanisms occurring within an organisms' lifetime. Although I unify them under a generic definition, these understandings are not suitable for studies at the intergenerational level. To fill this gap, I propose an inclusive understanding of epigenetics incorporating all the processes of parent–offspring resemblance that are not engraved into the DNA sequence. By integrating all mechanisms of phenotypic variation beyond the DNA sequence, this new understanding fully corresponds to the etymological meaning of the term "above, or beyond the gene." By integrating knowledge at all levels, this broader understanding of epigenetics should help transferring all the knowledge at the infra-individual level into the study of processes unfolding at the supra-individual level to build a continuum from molecules to ecology and evolution. Concepts of inheritance and early in life effects should play a major role in building such a continuum. Classifying more than 50 definitions of epigenetics in four groups using the actual terms of the definitions reveals interesting discrepancies between definitions and ultimate scientific goals. Finally, I present some examples of how a clear vision of the various understandings of epigenetics may influence biology and argue that epigenetics now needs to percolate in ecology and evolution.

E. Danchin (✉)
Laboratoire Évolution and Diversité Biologique (EDB UMR 5174), CNRS, Université de Toulouse, IRD, Toulouse Cedex 9, France
e-mail: etienne.danchin@univ-tlse3.fr

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1.1 Introduction

The term early in life effects qualifies instances when environmental factors acting on organisms during their early development are the most efficient in deeply and lastingly affecting the resulting adult's phenotype. One goal of this chapter is to present and discuss the current knowledge on the molecular mechanisms responsible for these effects. Today, it is relatively well accepted that epigenetic change constitutes the major molecular process underlying all phenotypic plasticity and accommodation changes that mediate early in life effects. This is either implicit or explicit in most if not all the chapters of this book. However, different authors have different understandings of the term epigenetics (see below and Jablonka and Lamb 2002) and do not necessarily incorporate into this concept the same range of molecular mechanisms. Although this diversity of meanings and spans of the epigenetic concept constitutes its richness, a bit like this is the case for the biological concepts of fitness or information, it is nonetheless necessary to clarify the various understandings of this concept to avoid misunderstandings on its role in early in life effects. In this chapter, I adopt an historical perspective to identify the two major categories of understandings of the term epigenetics. I further propose two complementary understandings, one of which might be particularly useful for eco-evolutionary approaches, and one stressing the unifying deep molecular nature of all epigenetic processes.

The term epigenetics has a long history during which its general meaning changed. In biology, the term was popularized by Conrad Waddington in the context of genetic assimilation (see glossary and Waddington 1939, 1942). Note, however, that at that time the term genetic was not DNA sequence based and meant anything inherited (see Glossary). For Waddington, the term epigenetics highlighted the role of epigenesis (development) in phenotype formation. It encompassed all the causal processes of development occurring beyond the sole effect of genes (see also Jablonka and Lamb 2002; Van Speybroeck 2002; Haig 2004; Felsenfeld 2014; Nicoglou and Merlin 2017). For Waddington the term epigenetics had the potential to reconcile epigenesis, genetics, and evolution (Richards 2006; Nicoglou 2018). At that time, it did not necessarily focus on molecular mechanisms. Since that era, the meaning of the term epigenetics has gradually moved away from the original Waddingtonian motivation to become more and more molecular (Jablonka and Lamb 2002; Richards 2006; Bird 2007; Table 2 in Skinner et al. 2010) with a meaning now equivalent to "epi (above and by extension beyond)–genetics."

This trend accelerated with the development of high throughput sequencing at the turn of the millennium. These fantastic technological developments made it clear that the complexity of living organisms could not be fully explained by the sole information encoded into the DNA sequence of coding genes (Jablonka et al. 1998; Maher 2008; review in Danchin et al. 2019b). It appeared that even the most refined description of genetic variation could not fully explain the measured inheritance of the concerned trait in populational or epidemiological studies. This fostered a debate about the existence of missing heritability and its causes (Maher 2008; Danchin

2013; Bourrat et al. 2017; Bourrat and Lu 2017). As a consequence, today, many authors agree that the idea that inheritance mainly, if not exclusively, rests on the transmission of DNA sequence (i.e., the sequencic vision of inheritance, see Glossary), needs to be revisited and extended (e.g., Muller 2007; Pigliucci 2007; Pigliucci 2009; Helanterä and Uller 2010; Pigliucci and Müller 2010, reviews in Danchin et al. 2011; Bonduriansky 2012; Mesoudi et al. 2013; Laland et al. 2015; Huneman and Whalsh 2017; Lu and Bourrat 2017; Merlin and Riboli-Sasco 2017; Muller 2017; Uller and Helanterä 2017; Wang et al. 2017; Bonduriansky and Day 2018; Danchin et al. 2019b).

Today, a generic definition is that epigenetics encompasses the various molecular bearers of information that are independent from that engraved into the DNA sequence of nucleotides (Heard and Martienssen 2014). It usually includes three categories of mechanisms, namely (i) chemical change in the DNA (methylation, acetylation), (ii) histone modifications and substitutions, and (iii) the evermore prominent role of small non-coding RNAs (Brinkman and Stunnenberg 2008; Khalil and Wahlestedt 2008; Skinner et al. 2010; Mazzio and Soliman 2012; Chen et al. 2016b; Tollefsbol 2017; Wang et al. 2017; Danchin et al. 2019b).

Furthermore, the history of epigenetics interacts with that of non-genetic inheritance, which encompasses all inclusively heritable information that is not encoded into the DNA but that nonetheless participates to parent–offspring resemblance, i.e. to heredity. This field, that emerged as a central domain of evolutionary biology during the last decades, plays a major role in the study of early in life effects as many forms of biological memory—beyond DNA sequence—participate to these effects, and need to be incorporated into our analysis of heredity.

In this context, while the molecular basis of epigenetics is relatively well investigated, their ecological and evolutionary implications are less explored despite Waddington's and followers' claims about their evolutionary importance (e.g., Waddington 1953b, 1959). Usually epigenetic processes are viewed as having evolved with multicellularity for cell differentiation (Willbanks et al. 2016). However, epigenetic processes are probably much more ancient because they exist in bacteria and unicellular eukaryotes (Jablonka and Lamb 2005) where they play a role in adaptation to the environment (Brooks et al. 2011), and possibly in immunity against the most common parasite of those organisms, namely pieces of DNA (Jablonka and Lamb 2005).

Here, I review the various understandings of the term epigenetics with a historical and conceptual perspective. In doing so, I briefly describe how epigenetic states often constitute a transgenerational form of biological memory that can play a major role in adaptation to environmental change and more generally in biology, particularly when activated early in life (see also a suit of reviews among which Jablonka and Lamb 1989, 1995, 2005; Jablonka et al. 1998; Jablonka and Raz 2009; Wang et al. 2017; Bonduriansky and Day 2018; Danchin et al. 2019b). I then propose a generic definition of epigenetics centered on its most basic characteristics. Based on previous observations that the meaning of epigenetics often covers a broader spectrum of processes (Jablonka and Lamb 2002), I finally propose a third understanding (the inclusive understanding) of epigenetics that places early in life effects at the

heart of evolutionary processes and that should be particularly relevant to ecological and evolutionary studies. I argue that epigenetics needs to become an important theme of research in all domains of biology. Using an objective methodology, I then classify a sample of more than 50 published definitions of epigenetics into the developmental (itself with two sub-categories) and the evolutionary understanding of epigenetics. I also define a category encompassing all ambiguous definitions making it impossible to attribute them to one of the two classical categories. I finally discuss some of the applications of the new proposed understanding of epigenetics.

1.2 The Developmental Understanding of Epigenetics

Although almost all cells within a multicellular organism have the same sequencic information, they nonetheless exhibit contrasting phenotypes, such as neurons, bone, liver, skin, or lung cells. For instance, a human body contains about 200 different cell types. Furthermore, these characteristics are highly stable as differentiated cells almost exclusively produce daughter cells of the same type, thus generating lineages of same-type-cells. This raises the enigma of how such cell differentiation can occur. When, in the 1930s, Waddington used and defined the adjective epigenetic, his purpose was to answer that specific question.

In the 1950s, David Nanney (Nanney 1958) proposed a theoretical hypothesis. He suggested that the same genotype could be associated with different phenotypes because of the activity of mitotically stable "epigenetic control systems" regulating gene expression, a phenomenon today called "cellular memory," which is central to development and life. Nanney thought that most epigenetic control systems were situated in the cytoplasm, while today, we know that such variation in gene expression among cell lineages results from factors acting mainly, but not exclusively, within the nucleus.

The 1960s and 1970s saw a further connection between molecular epigenetics and cellular differentiation with the documentation of the link between chromatin state (heterochromatin and euchromatin) and gene expression, and the discovery of how the DNA is structured in nucleosomes. In 1975, two teams independently proposed that chemical modifications of the DNA (such as DNA methylation) may associate with gene expression (Riggs 1975; Pugh and Holliday 1978). For them, the DNA methylation patterns were "heritable" (i.e., copied in mitosis), potentially explaining cellular memory. The connection with epigenetics appeared a few years later in Holliday's paper on carcinogenesis (Holliday 1979). Pugh and Holliday had previously commented the debate on whether carcinogenesis has a mutational or epigenetic basis (Pugh and Holliday 1978). They suggested that "the methylated state of particular DNA sequences could stably control gene expression" as during development. Therefore, changes in gene expression following a mutation may not result from a mutation per se, but from the resulting epigenetic changes that in turn provoke a stable change in gene expression (Pugh and Holliday 1978).

The study of histone modifications and DNA methylation only converged in the 1990s (Deichmann 2016), and Holliday also specified his definition of epigenetics, including (i) changes in gene expression among differentiated cells and (ii) the transmission of these changes during mitosis (and possibly meiosis (Holliday 1994)). Finally, a general definition of epigenetics at the molecular and cellular level emerged as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (p. 1 in Russo et al. 1996) [Note, however, that at that time, they used the term "meiotically heritable change", while it is now known that this is not always the case (Heard and Martienssen 2014), making the term "meiotic" rather inappropriate as epigenetic information may bypass meiosis]. That definition had three major features: (1) cellular memory enabled through mitotic and/or meiotic cell divisions; (2) the effect produced on gene expression; (3) changes do not involve DNA sequence mutations. Today, that definition still constitutes a generic template to most definitions of epigenetics.

However, the reference to cellular memory currently tends to loosen. For instance, with histone chemical modifications and the role of small non-coding RNAs, the term epigenetics has been used to refer to any modification other than change in DNA sequence affecting gene expression, *whether those modifications are stable or not during cellular divisions*. Thus, while cellular memory is central for development, it is sometimes considered as secondary for epigenetics, leading to incorporate into epigenetics any temporary variation that is not of sequencic origin.

In conclusion, the developmental understanding of epigenetics focuses on infra-individual processes (see Glossary) and traditionally mainly concerns complex multicellular organisms, although today the field also incorporates unicellular organisms. In this understanding, epigenetics refers to chromatin modification, DNA methylation, acetylation and other histone chemical modifications, small non-coding RNAs and the way they stably influence gene expression. Today, this understanding of epigenetics mostly looks at molecular marks and signals that affect cellular phenotypes within an organism, thus neglecting physiological aspects, such as metabolism and physico-chemical reactions at higher levels of organization (cell, tissue, and organism).

1.3 The Evolutionary Understanding of Epigenetics

The second major understanding of epigenetics is "the evolutionary understanding" that integrates epigenetics into the study of inheritance and evolution. Its premises are to be found in evolutionary developmental biology (Evo-Devo). However, although the initial goal of Evo-Devo was to integrate the role of development as a major component of adaptation and evolution, it never achieved that goal because it mainly reduced the Evo part to the accounting of the sequencic information into the study of development. In this sense, Evo-Devo is an important part of the Modern Synthesis of Evolution.

The evolutionary understanding of epigenetics really emerged following the discovery that some recently acquired plastic responses can persist intergenerationally, correlatively with epigenetic marks, implying that some epigenetic marks can somehow percolate across generations and participate to heredity. Historically, the concept of epigenetic inheritance states that some chromatin modifications affecting gene expression can be highly stable not only across mitosis, but also across the reproduction of multicellular organisms, potentially being maintained across many generations (Holliday 1994; Russo et al. 1996; Skinner 2011b). In effect, some epigenetic marks persist across generations of cells during development of multicellular organisms. This is why mother and daughter cells are of the same type (such mitotic stability is sometimes called "heritability," e.g., Skinner 2011b). The link with inheritance clearly emerged following the discovery that these stringent properties of persistence at the infra-individual level sometimes percolate across generations and thus participate to inheritance of multicellular organisms (reviews Mameli 2004, sometimes, surprisingly, over more than 80 generations Vastenhouw et al. 2006; Bonduriansky and Day 2009; Danchin and Wagner 2010; Pigliucci and Müller 2010; Danchin et al. 2011; Bonduriansky 2012; Danchin 2013; or 25 generations Devanapally et al. 2015; Chen et al. 2016a; Wang et al. 2017; Danchin et al. 2019b). Therefore, the focus of many biologists progressively shifted from the study of epigenetics in development to the role of epigenetics in evolution. This second understanding rests on the same mechanisms as the developmental understanding, but differs from it mainly in its ultimate target, namely inheritance and evolution rather than development.

Today, it is becoming more and more accepted that transgenerational epigenetic states can participate to parent–offspring resemblance (i.e., to heredity), in a form of epigenetic intergenerational inheritance, with all its evolutionary implications (Danchin et al. 2011; Grossniklaus et al. 2013; recent reviews in Jablonka 2013; Norouzitallab et al. 2014; Singh et al. 2014; Szyf 2014; Bohacek and Mansuy 2015; Wang et al. 2017; Danchin et al. 2019a, b). Evidence keeps on accruing at a fast pace (Devanapally et al. 2015; Sharma 2015; Szyf 2015; Tricker 2015; Chen et al. 2016a; Sharma et al. 2016), fostering the emergence of a new domain of epigenetics studying the role of epigenetics in heredity and evolution. Consequently, the mainstream vision of evolution (i.e., the Modern Synthesis of Evolution) that mainly, if not exclusively, considers DNA sequence variation as the sole source of heritable variation (i.e., parent–offspring resemblance), needs to be revised in order to incorporate the epigenetic source of heritable variation (Pennisi 2008; Pigliucci and Müller 2010; Laland et al. 2014, 2015).

In this context, more and more studies now focus on mechanisms of epigenetic inheritance and their potential evolutionary consequences (e.g., West-Eberhard 2003; Bonduriansky and Day 2009; Bonduriansky 2012; Geoghegan and Spencer 2012; Grossniklaus et al. 2013). An increasing number of authors, among which Eva Jablonka and collaborators, started to call for an evolutionary understanding of epigenetics (Jablonka and Lamb 1989, 1995, 2005; Jablonka and Raz 2009; Pigliucci and Müller 2010; Jablonka and Lamm 2011; Jablonka 2013; Huneman and Whalsh 2017). In this context, Jablonka and followers claim that epigenetic

transmission across generations of organisms challenges the traditional evolutionary theory, and calls for an Extended Evolutionary Synthesis (Pigliucci and Müller 2010; Laland et al. 2015).

To sum up, the evolutionary understanding of epigenetics, beautifully illustrated in Jablonka's work, although mainly relying on the infra-individual developmental approaches nonetheless goes beyond the lifecycle of individual organisms by tackling issues linked to epigenetic stability. In doing so, it sets the stage for the study of the consequences of epigenetics in evolution. However, this evolutionary understanding does not explicitly incorporate the wealth of populational concepts coming from disciplines, such as behavioral ecology, population dynamics, population and quantitative genetics into epigenetic studies (Danchin and Pocheville 2014). In other words, the evolutionary understanding of epigenetics has not really tackled the question of how epigenetic stability quantitatively translates into epigenetic inheritance, and its consequences at the supra-individual level (see Glossary). Furthermore, by focusing on the molecular basis of epigenetics (belonging to the infra-individual level approach), the evolutionary understanding of epigenetics may ignore non-molecular transmission modes, such as cultural and ecological inheritance. While the idea that epigenetic states can be passed on across generations emerged from the epigenetic literature, the extent to which this participates to inclusive heritability (see Glossary) and evolution has not been explicitly investigated yet. Such questions are particularly relevant to evaluate the evolutionary potential of epigenetic inheritance, and, more generally, how natural populations respond to selection. This suggests that we still need a more ambitious definition of epigenetics.

1.4 The Deep Nature of Epigenetics Under These Two Understandings

These two modern understandings of epigenetics rest on the same set of three major molecular mechanisms, namely (1) chemical change in the DNA (methylation, acetylation), (2) histone modifications, and (3) the role of small non-coding RNAs. While the two first processes directly produce changes in the DNA packaging within the cell nucleus, the third one constitutes more a media allowing part of an organism to affect gene expression within other parts of the body (soma and/or germline), thus mimicking hormones (Danchin et al. 2019a).

1.4.1 The Four Major Timescales of DNA Packaging Affecting Gene Expression

In effect, altogether, these processes modify the closing or opening of the chromatin (that is the packaging of the DNA molecule) of specific portions of the genome, which in turn affects the accessibility of the DNA sequence to the molecular machinery of gene expression. In other words, they change the 3D structure of the DNA. The resulting changes in gene expression are active at four very different time scales ranging from seconds up to hundreds and potentially thousands of generations or more, and that, as far as we know, are orthogonal to the three types of molecular mechanisms summarized in the previous paragraph. These contrasted timescales are:

- On the short-term, these processes fine-tune gene expression to accompany everyday cell metabolism in a transitory way.
- On the mid-term, they affect gene expression up to over the whole life of an organism in order to allow cell differentiation (development), as well as acclimation to current environmental conditions (plasticity). This is also the main timescale of early in life effects.
- On the long-term, they participate to inheritance in multicellular organisms, a process that emerges from some of the mid-term epigenetic processes including early in life effects.
- On the very long term of hundreds and thousands of generations, they may also facilitate the sequencic engraving of the corresponding adaptations (Danchin et al. 2019b).

Today, we still do not know the mechanisms responsible for such big differences in stability. The developmental and the evolutionary understandings of epigenetics only concern mid- and long-term processes, respectively, in that they both stress the importance of the stability of changes in DNA packaging. These two understandings thus mainly differ in their temporal scales. The developmental understanding focuses on intra-individual processes at the mid-term scale, while the evolutionary understanding concerns the larger timescale of transgenerational processes.

1.4.2 A Parallel with the Study of Proteins

Concerning the information carried out by the DNA molecule, there is an interesting parallel to be drawn with the study of proteins. After spending much energy in studying protein amino acid sequences, it appeared that their functional properties mostly result from their general shape. The latter is indeed influenced by the sequence of amino acids (called the primary structure), but also by the way the amino acid chain folds into a spiral (secondary structure), and at a larger scale by the way that spiral folds into its 3D shape (tertiary structure). Although the sequence of amino acids strongly influences protein shape, other factors determine the final 3D

structure of the resulting protein, and thus their biological function. In particular, environmental stresses can affect proteins' 3D shape, so that a given amino acid chain can lead to different shapes, some that are biologically functional and others that are not. Prion diseases are disorders that result from protein misfolding following environmental stress. These diseases result from the capacity of prions to serve as the ill-folding template for similar proteins leading to the propagation of their ill shape and their accumulation. Chaperon proteins—specific proteins that help maintaining other proteins in their functional shape—protect against such disorders, particularly after specific stresses such as heat shocks.

The same holds for DNA, in which the sequence provides some information, but the 3D structure ensures that information is used at the right place and at right time. Thus, ignoring the 3D structure of the DNA—which is the essence of the sequencic vision of DNA information—cannot allow us to understand life in all its complexity, and would be comparable to only studying protein amino acid sequences to understand their functions, which would lead us to misunderstand a good deal of their basic roles in life.

Nonetheless, as I do here and in my previous papers, I recommend to clearly separate the sequencic from the 3D components of the information carried out by the DNA molecule because they have drastically different properties and therefore play contrasting but complementary roles in evolution (Danchin et al. 2019a). The central point is that we should not forget the importance of these *two* components, genetics *and* epigenetics, in accommodation, inheritance, adaptation, and evolution.

1.4.3 Epigenetics: The Science of the 3D or Even 4D Structure of DNA

The above two main understandings of epigenetics are unified by the fact that they stress the importance of the 3D structure of the DNA molecule in metabolism, development, and evolution, beyond its sequencic information. A unifying definition of epigenetics can thus be that it is the science *of DNA 3D structure that is stable enough to persist across mitosis or generations.*

In fact, we can go beyond that 3D definition by incorporating the temporal dynamics of gene expression as a major fourth dimension of epigenetics. Indeed, the translation of mRNAs into proteins is strongly regulated by a range of factors, some of which are under environmental control.

A first factor involves synonymous codons. The genetic code is redundant in the sense that many amino acids can be coded by several "synonymous" codons. However, for a given organism, one of these codons is predominantly used to encode a given amino acid, the other codons being much rarer (this is the codon usage bias, Frumkin et al. 2018; Yang et al. 2019). Rare synonymous codons significantly affect the function of the concerned protein in slowing down, or even stopping prematurely, the translation of mRNA into protein in the ribosomes (Yang et al. 2019).

Rare codons can also influence the resulting folding of proteins, hence affecting their biological function. As a result, the protein is not produced at the right time to fulfill its function. For example, in *Escherichia coli*, disruption of the kinetics of synthesis of a highly expressed protein induced by a rare synonymous codon can decrease the efficiency of translation and reduce the bacterium's fitness (Frumkin et al. 2018). Thus, although synonymous codons code for the same protein sequence, the dynamics of protein synthesis may affect their biological function, thus introducing another source of phenotypic variation. This highlights the importance of the kinetics of protein synthesis and the fact that different kinetics generate variation due not to the 3D shape of the DNA, but to the fourth dimension of the dynamics of protein synthesis.

Furthermore, the regulation and efficiency of the translation of mRNAs into protein is also strongly influenced by numerous environmentally induced modifications of mRNAs or tRNAs that, by affecting the initiation of translation and the dynamics of codon–anticodon interactions, accelerate, stop, or slow down protein synthesis, thus affecting the phenotype [for modifications of tRNAs or mRNA, see Leppek et al. (2018); Ranjan and Leidel (2019), respectively]. The resulting variations in kinetics can affect the phenotype and, in particular, the health of organisms.

Many of such changes are influenced by environmental stresses (Leppek et al. 2018; Ranjan and Leidel 2019), and participate to phenotypic plasticity, producing variation in functional gene expression that is independent of sequencic variation. If these effects are transmitted during mitosis or between generations of multicellular organisms, they would belong to epigenetics. I do not know papers reporting the transmission of mRNA translation regulatory states during mitosis or between generations. However, this absence may only reveal the fact that these processes have been described too recently. The large international project on the dynamics of genome conformation in space and time (3D and 4D) might show that some of these processes are transmitted either in mitosis or across generations (Dekker et al. 2017).

Anticipating such discoveries, I propose a more complete definition focusing on the functional nature of epigenetics, which would be *the science of the 3D, or even 4D, structure of the DNA that is stable enough to persist across mitosis or generations of multicellular organisms beyond sequencic.* This definition of course includes all the 3D aspects related to the shape of nucleic acids within chromatin, but also all the components of the dynamics of gene expression itself, which, via its effects on the efficiency of gene translation, can influence phenotypic fitness.

This unified vision of epigenetics is in fact at the heart of several non-genetic inheritance systems. It is also at the heart of the study of early in life effects and of precision (or individualized) medicine. We can even envision the chromatin as a kind of gigantic prion as not only the DNA sequence is transmitted but also a significant part of its 4D structure.

This unified vision of epigenetics claims that the sequencic vision of life, by focusing only on sequence information, has made us blind to the information encoded into the 3D and 4D structure of the DNA. The sequencic vision of inheritance in effect led us to discard part of inheritance processes on the sole

basis of the fact that it is not engraved into the DNA sequence (Danchin et al. 2011; Danchin 2013).

1.5 The Inclusive Understanding of Epigenetics

The above-unified definition of epigenetics constitutes a step forward toward the integration of epigenetics within the Extended Evolutionary Synthesis (e.g., Pigliucci 2007; Pigliucci and Müller 2010; Huneman and Whalsh 2017; Muller 2017; Bonduriansky and Day 2018). However, I think that this constitutes only a first step in the necessary modernization of the Modern Synthesis of Evolution (see, for instance, Danchin et al. 2019a). I now discuss the necessity to go farther by transposing concepts of epigenetics into eco-evolutionary studies, and vice versa, which implies the use of a fourth understanding of epigenetics based on a generalized meaning of epigenetics, integrating all forms of non-genetic inheritance into the study of eco-evolutionary dynamics. Such a definition puts early in life effects at the center of the concept of epigenetics. In doing so, I follow and amplify the approach of previous authors such as Jablonka and Lamb who had already observed that "*the examination of recent books and articles with epigenetics in their titles show that the scope of the subject is far less narrow than some current definitions suggest*" (Jablonka and Lamb 2002). My aim here is to confirm this state of affairs by fully endorsing the implicit and more or less unacknowledged existence of this very general vision of epigenetics, which proves to be particularly well suited to medical, ecological, and evolutionary studies.

1.5.1 Injecting Eco-Evolutionary Concepts into Epigenetics

The scale change from infra- to supra-individual biology that I have been advocating implies injecting processes relevant at the scale of individuals, populations, and ecosystems into the definition of epigenetics. For that goal, a populational concept such as inclusive heritability (with its sequencic and non-sequencic components, the latter including early in life effects) is particularly relevant for several reasons (Danchin and Pocheville 2014; Pocheville and Danchin 2015).

First, when Darwin talked of heredity (see Glossary and Danchin and Wagner 2010; Danchin et al. 2011, 2019a) in saying that, "*Any variation which is not inherited is unimportant for us*" (p. 12 in Darwin 1859), he had an all-inclusive vision of inheritance, and claimed that what we now call inclusive heritability is central to evolution by natural selection. In modern language, the above quote can be rephrased in "for a trait to evolve by selection (whether natural, artificial or drift) it must be inclusively heritable, i.e. offspring must resemble their parents." This statement is independent from the mechanisms underlying resemblance. What matters is that a value of a trait be stable transgenerationally. Thus, the concept of

heritability is keystone in any evolutionary synthesis, and initially (i.e., at the time of Darwin) incorporated what we now call epigenetic inheritance alongside with many other processes that we are currently rediscovering, such as cultural and ecological inheritance.

Second, the fact that the concept of 'heritability' has been used (see Table 1.1) both in infra- and supra-individual approaches suggests that it has some relevance to both domains (Danchin and Pocheville 2014; Pocheville and Danchin 2015). Although historically developed at the population level (supra-individual), the concept of heritability thus appears to have some relevance to study the molecular basis of parent–offspring resemblance (infra-individual). In this sense, the concept of heritability (including its epigenetic component, as well as all other processes of parent–offspring resemblance) has the potential to bridge the infra- and supra-individual approaches, the latter concerning ecologists, as well as population and evolutionary biologists (Danchin and Pocheville 2014; Pocheville and Danchin 2015).

Third, confronting the sequencic and populational approaches of heritability revealed an inconvenient but interesting discrepancy between these two approaches. At the sequencic level, the most fine-grained descriptions of within-population genetic variation [sometimes involving millions of Single Nucleotide Polymorphisms (SNPs) in what is usually called Genome Wide Association Studies or GWAS] led to estimates of genetic heritability that were surprisingly low relative to the estimates calculated for the same trait at the populational level in ecology or epidemiology (i.e., the supra-individual level). This recurrent formidable discrepancy, which has been dubbed "missing heritability" (Maher 2008), raised considerable debates. To illustrate the intensity of the ongoing debates, while the expression "missing heritability" first appeared in 2008, searching for that term produced 1849 hits on the web of knowledge, and 19,100 hits in Google Scholar (Fig. 1.1). Missing heritability strongly suggests that the weight of non-genetic inheritance might be much higher than usually anticipated as the observed discrepancy may be partly because populational estimates of heritability in effect capture a good deal of non-genetic inheritance effects (Danchin 2013, Bourrat et al. 2017, Bourrat and Lu 2017).

Fourth, a striking characteristic of many identified mechanisms of non-genetic inheritance (reviews in Mameli 2004; Danchin et al. 2004, 2011, 2019b; Bonduriansky and Day 2009; Danchin and Wagner 2010; Pigliucci and Müller 2010; Bonduriansky 2012; Danchin 2013; Wang et al. 2017) is that they involve molecular processes classically viewed as developmental processes. For instance, epigenetics constitutes a major developmental hub in that resemblance involves transmitted epigenetic changes (which in turn can affect the stability of the DNA sequence, Danchin et al. 2019b). Similarly, social learning is a developmental process potentially leading to cultural transmission and parent–offspring resemblance under some specific conditions (Danchin et al. 2018). This underlines the existence of a continuum between infra- and supra-individual processes.

Fifth, many non-genetic processes of inheritance result from strong early in life effects, to the point that it might well be that the earlier in life an effect occurs, the

Table 1.1 From more than fifty to five shades of epigenetic gray to only five shades. A list of more than 50 definitions of epigenetics from the literature, including two new definitions. This constitutes a small subsample of existing definitions (others can be found in Jablonka and Lamb 2002). All texts in the definition column are quotes. The classification is based only on the terms found in the definition of epigenetics, independently form the context and goals of the concerned study. Definitions are grouped according to the method described in the text, and chronologically within groups. Terms like "heritable," "inheritance," "stable," or "perpetuate" often appear in definitions without specifying the timescale of the stability. Under the first understanding of along-asexual-cell-lineages, the definition should be classified as "Developmental definitions 2." Under the second understanding of along-generations-of-sexually-reproducing-organisms, it would be classified as "Evolutionary." All such ambiguous definitions are grouped under the Ambiguous group, and ambiguous term is underlined. Legend of shades of gray: **D1 in grayish white**: Group of Developmental definitions 1; **D2 in light gray**: Group of Developmental definitions 2; **A in light gray**: Group of Ambiguous definitions; **E in dark gray**: Group 2 of Evolutionary definitions; **I in black**: Group of Inclusive definitions

Definition	Reference	Shades of Epigenetic Grey
Developmental definitions 1		
Changes in genotypes only have ostensible effects in evolution if they bring with them alterations in the **epigenetic processes by which phenotypes come into being**; [bold text by chapter's author].	(Waddington 1953a)	**D1**
The science of developmental process in general (…). The analytical study of development "including the problem of" cellular differentiation.	(Huxley 1956)	**D1**
Epigenetic control systems are "auxiliary mechanisms with different principles of operation involved in determining which specificities are to be expressed in any particular cell".	(Nanney 1958)	**D1**
(…) a suitable name for the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.	(Waddington 1968)	**D1**
In the modern usage, epigenesis stands for all the processes that go into implementation of the genetic instructions contained within the fertilized egg. "Genetics proposes: epigenetics disposes".	(Medawar and Medawar 1983)	**D1**
Epigenetics is concerned with the strategy of the genes in unfolding the genetic program for development.	(Holliday 1987)	**D1**
Generally speaking, epigenetic states or epigenetic regulation refer to situations in which several states of gene expression may coexist in similar environmental conditions, despite the absence of significant changes in the genomic sequence.	(Thieffry and Sanchez 2002)	**D1**
Epigenetic (…) has come to refer to the changes in chromatin and DNA structure which alter gene expression and hence phenotype that do not involve changes to the sequence of DNA.	(Champagne 2008)	**D1**
The study of emergent properties in the origin of the phenotype in development and in modification of phenotypes in evolution.	(Hallgrímsson and Hall 2011)	**D1**
Epigenetics or epigenetic control is the sum of the genetic and non-genetic factors acting upon cells to selectively control the gene expression that produces increasing phenotypic complexity during development.	(Hall 2012)	**D1**
What Waddington called developmental constraints and epigenetics can now be identified as the layers of molecular regulatory networks and cell-cell communication networks – a web of interactions through which genomic information must percolate to produce the macroscopic phenotype.	(Huang 2012)	**D1**
Epigenetics is a mechanism of gene transcription regulation that does not change the DNA sequence and is usually reversible.	(Willbanks et al. 2016)	**D1**
Developmental definitions 2		
(…) the study of mechanisms of temporal and spatial control of gene activity during the development of complex organisms. (…). Mechanisms of epigenetic control must include the inheritance of a particular spectrum of gene activities in each specialized cell. In addition to the classical DNA code, it is necessary to envisage the superimposition of an additional layer of information which comprises part of the hereditary material, and in many cases, this is very stable. The term epigenetic inheritance has been introduced to describe this situation.	(Holliday 1990)	**D2**

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
The study of the changes in gene expression, which occur in organisms with differentiated cells, and the mitotic inheritance of given patterns of gene expression.	(Holliday 1994)	**D2**
Imagine, therefore, my surprise in learning that "epigenetics" will ultimately be understood as the study of changes in gene function that are heritable and that do not entail a change in DNA sequence!	(Wu and Morris 2001)	**D2**
Epigenesis concerns the interactions through which the inherited potentials of the genome become actualized into an adult organism.	(Gilbert 2002)	**D2**
The term 'epigenetics', which literally means 'outside conventional genetics', is now used to describe the study of stable alterations in gene expression potential that arise during development and cell proliferation.	(Jaenisch and Bird 2003)	**D2**
That 'something else' is chemical modifications of genes that are heritable from one cell generation to the next and that affect gene expression but do not alter the DNA sequence.	(Bradbury 2003)	**D2**
Epigenetic alterations involve information heritable during cell division other than the DNA sequence itself.	(Bjornsson et al. 2004)	**D2**
Although several definitions for epigenetics have been proposed, the term epigenetics refers to changes in gene expression which can be maintained through cell divisions and are not coded in the DNA sequence itself.	(Khalil and Wahlestedt 2008)	**D2**
Epigenetics is the study of the processes that underlie developmental plasticity and canalization and that bring about persistent developmental effects in both prokaryotes and eukaryotes.	(Jablonka and Raz 2009)	**D2**
Epigenetics is the study of heritable changes in gene expression that occur without changes in DNA sequence. Epigenetic mechanisms are flexible genomic parameters that can change genome function under exogenous influence, and also provide a mechanism that allows for the stable propagation of gene activity states **from one generation of cells to the next.** [bold text by chapter's author]	(Bollati and Baccarelli 2010)	**D2**
Molecular factors and processes around DNA that are mitotically stable and regulate genome activity independent of DNA sequence.	(Skinner et al. 2010)	**D2**
(…) molecular factors or processes around DNA that regulate genome activity independent of DNA sequence and that are mitotically stable.	(Skinner 2011a)	**D2**
Epigenetics is defined today as the study of the mechanisms that lead to 'persistent' developmental changes in gene activities and effects, but do not involve altered DNA base sequences.	(Jablonka and Lamm 2011)	**D2**
Here we employ the term [epigenetics] in the more conservative sense that concerns the perpetuation of gene expression and function across cell divisions without changes in DNA sequence.	(Heard and Martienssen 2014)	**D2**
Epigenetics is defined as molecular factors and processes around the DNA that regulate genome activity independent of DNA sequence, and are mitotically stable.	(Guerrero-Bosagna and Skinner 2014)	**D2**
Epigenetics, the study of mitotically heritable and reversible molecular information outside of the DNA sequence (…).	(Ladd-Acosta and Fallin 2016)	**D2**
Epigenetics is the study of various intracellular factors that have an effect on the stability of developmental processes through their action on genome potentialities (i.e., the genome susceptibility to be differentially expressed).	(Nicoglou and Merlin 2017)	**D2**
Epigenetics focuses on mechanisms that govern accessibility to genetic information, independently of changes in DNA sequence. The establishment and maintenance of epigenetic profiles are essential for cell lineage determination and differentiation.	(Schang et al. 2018)	**D2**

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
Ambiguous definitions		
Epigenetic mechanisms, which involve DNA and histone modifications, result in the heritable silencing of genes without a change in their coding sequence.	(Egger et al. 2004)	A
The current use of the term epigenetics emphasizes heritable changes in gene expression that cannot be tied to genetic variation. (…) a positive definition has been proposed that equates epigenetic regulation with the active perpetuation of local chromatin states.	(Richards 2006)	A
Epigenetics refers to heritable changes in gene function that cannot be explained by changes in DNA sequence, with DNA methylation patterns being an important contribution to epigenetic memory.	(Pembrey et al. 2006)	A
The following could be a unifying definition of epigenetic events: the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states.	(Bird 2007)	A
Epigenetics, in a broad sense, is a bridge between genotype and phenotype—a phenomenon that changes the final outcome of a locus or chromosome without changing the underlying DNA sequence. (…) More specifically, epigenetics may be defined as the study of any potentially stable and, ideally, heritable change in gene expression or cellular phenotype that occurs without changes in Watson-Crick base-pairing of DNA.	(Goldberg et al. 2007)	A
Epigenetics refers to the heritable, but reversible, regulation of gene mediated principally through changes in DNA methylation and chromatin structure.	(Brinkman and Stunnenberg 2008)	A
We use the term epigenetics to classify those processes that ensure the inheritance of variation (-genetics) above and beyond (epi-) changes in the DNA sequence.	(Bonasio et al. 2010)	A
(…) the concept of epigenetics is relatively simple in that it describes a means by which genes are either turned on or off by a heritable epigenome.	(Mazzio and Soliman 2012)	A
Stable, heritable changes in gene expression can be caused by chromosomal modifications, exclusive of any alterations to the nucleotide sequence.	(Geoghegan and Spencer 2012)	A
Epigenetics is defined as the study of heritable changes in gene expression that are not linked to changes in the DNA sequence.	(Silveira et al. 2013)	A
Epigenetics refers to mechanisms of long-term or stable regulation of gene expression programs that do not involve a change in gene sequences.	(Szyf 2015)	A
Evolutionary definitions of epigenetics		
The study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.	(Russo et al. 1996)	E
Refers to the mitotic or meiotic transmissibility of chromatin variation, independent of DNA sequence variation.	(Johannes et al. 2008)	E
Epigenetics is defined as molecular factors and processes around DNA that regulate genome activity, independent of DNA sequence, and that are mitotically or meiotically stable.	(Skinner 2011b)	E

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
Epigenetics (…) is mainly used to describe modifications that cause changes in gene expression that are stably transmitted during mitosis or meiosis, but that do not involve differences in the underlying DNA sequence.	(Weigel and Colot 2012)	E
Epigenetics refers to changes in gene expression that occur through changes in DNA methylation, histone modification, small or micro-RNAs, or most inclusively, other mechanisms that alter how DNA sequences are translated into functional gene products. With the discovery that epigenetic modifications to gene expression can be inherited across cell lineages or even across organismal generations. (…)	(Donohue 2014)	E
(…) "Epigenetics is typically defined as the study of heritable changes in gene expression that are not due to changes in DNA sequence." However, this definition depends on what one means by "heritable." If one is thinking in terms of cells, it means that the gene expression pattern of one cell is transmitted accurately to that cell's descendants. (…). But (…), we are coming to realize how agents causing epigenetic changes in germ cells can create stable patterns of gene expression that become transmitted from an organism to its progeny.	(Gilbert and Epel 2015)	E
There is also increasing evidence for more stable transgenerational epigenetic inheritance, or the transmission across generations of cellular states without modification of the DNA sequence, which demonstrates that adaptive evolution may proceed by selection on epigenetic variants as well as variation in DNA sequence.	(Laland et al. 2015)	E
As currently defined, epigenetics deals with heritable, metastable and usually reversible changes that do not involve alterations in DNA sequence, but alter the way that information encoded in DNA is utilized. The bulk of current research in epigenetics concerns itself with mitotically inherited epigenetic processes underlying development or responses to environmental cues (as well as the role of mis-regulation or dysregulation of such processes in disease and ageing), i.e., epigenetic changes occurring within individuals. However, a steadily growing body of evidence indicates that epigenetic changes may also sometimes be transmitted from parents to progeny, meiotically in sexually reproducing organisms or mitotically in asexually reproducing ones.	(Manjrekar 2017).	E
The DNA of all higher organisms is subject to different chemical modifications that influence gene activity and expression, and that are summed up under the term 'epigenetics' (…) Earlier evidence of natural variation in DNA methylation, as well as of the inheritance and phenotypic effects of this epigenetic variation (…), led to several conceptual papers that suggested its potential **relevance to ecology and evolution** (…), and empirical work has been catching up slowly. Ecologists and evolutionary biologists are particularly interested in the unique contributions that epigenetic mechanisms might make. First, environment-sensitive epigenetic mechanisms could transmit responses to environmental changes across generation boundaries. Second, heritable epigenetic variants that arise stochastically, i.e. epimutations, that affect phenotypes may be under natural selection and might contribute to adaptation, independently from DNA sequence variation. [bold text by chapter's author]	(Richards et al. 2017)	E
Inclusively heritable molecular variation in gene expression without change in DNA sequence resulting from DNA methylation or histone modifications, and often mediated by small non-coding RNAs (sncRNAs, i.e. RNA molecules that are not translated into proteins and that are less than 200 nt in size).	(Danchin et al. 2019b)	E
The science of the 3D, or even 4D, structure of the DNA that is stable enough to persist across mitosis or generations beyond sequencic.	This book chapter	E
Inclusive definitions of epigenetics		

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
This term has now been somewhat redefined and although there are many variants of the definition of this term today, a consensus definition is that epigenetics is **the collective heritable changes in phenotype** due to processes that arise independent of primary DNA sequence. This heritability of epigenetic information was for many years thought to be limited to cellular divisions. However, it is now apparent that epigenetic processes can be transferred in organisms from one generation to another. [bold text by chapter's author]	(Tollefsbol 2017)	I
(…) epigenetics (i.e. non-DNA sequence-based rather than mutational) modifications. In this review, we summarize recent evidence on epigenetic inheritance from parental environment-induced developmental and physiological alterations (…). The epigenetic modifications demonstrated to be both susceptible to modulation by environmental cues and heritable, including DNA methylation, histone modification, and small non-coding RNAs, are also summarized. [bold text by chapter's author]	(Wang et al. 2017)	I
All the information bearers and processes of phenotypic variation (often involving environmentally driven variation in gene expression) that participate to parent–offspring resemblance, and that are not due to DNA nucleotidic sequence variation in the germline. This broad understanding incorporates the three classical molecular mechanisms of (i) chemical DNA modifications and (ii) histone modifications, and (iii) micro RNAs, as well as all other heritable processes of phenotypic variation, such as prions and chaperon molecules (…), cytoplasmic inheritance, parental effects, ecological inheritance, cultural inheritance, and the inheritance of the microbiota. It also incorporates DNA sequence variation that may arise in somatic cells, as in mammalian immunity. This all-inclusive understanding encompasses all the processes that can produce intergenerationally persistent phenotypic variation, thus participating to parent-offspring resemblance beyond the sole effect of genetics (sequencic). Hence, this understanding encompasses any process involved in heredity beyond genetics.	This book chapter	I

more likely it will be transmitted to subsequent generations and hence participate to inclusive heritability. This is, however, an entirely unexplored domain of the study of early in life effects.

All these characteristics make heritability (here understood in its inclusive meaning) particularly suitable for bridging properties at the infra-individual level with supra-individual processes (Danchin and Pocheville 2014; Pocheville and Danchin 2015). As epigenetics has emerged as a major mechanism of inheritance contributing to heritability, I now propose a definition of epigenetics that incorporates all the dimensions of inheritance beyond sequencic, which I call the inclusive understanding of epigenetics, with the goal of facilitating the merging with concepts used by ecologists and evolutionary biologists.

1.5.2 An Inclusive Definition of Epigenetics

In this context, an inclusive definition of epigenetics explicitly designed to help integrating the infra- with supra-individual levels could be *all the information bearers and processes of phenotypic variation (often generated by environmentally driven variation in gene expression) that participate to parent–offspring*

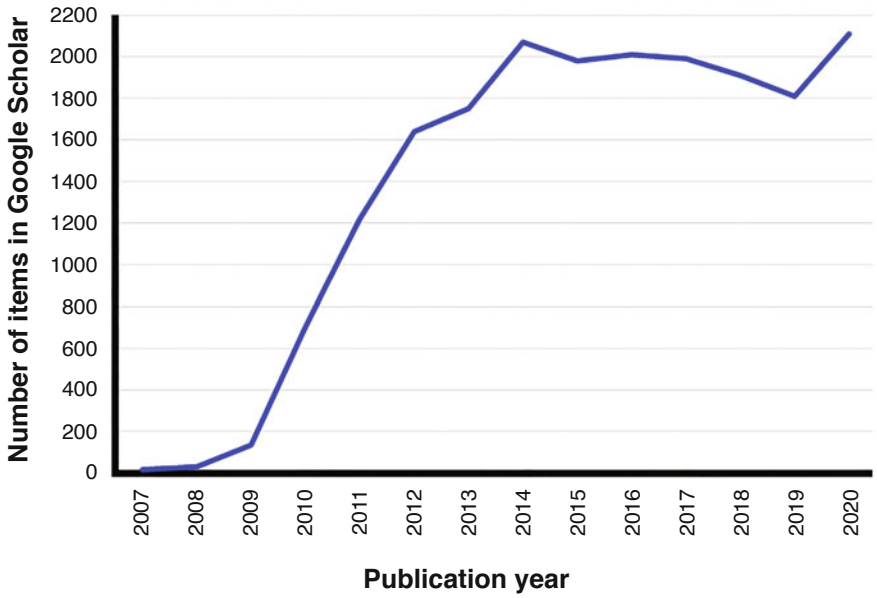

Fig. 1.1 Yearly number of hits for "Missing heritability" in Google Scholar. The first major paper was in 2008 (Maher 2008). Then the number of items dealing with missing heritability increased rapidly and stabilized around 2000 items per year in recent years. Data gathered on 19 April 2021

resemblance (i.e. that are inclusively heritable) and that are not due to DNA nucleotidic sequence variation in the germline.

This understanding is much broader than the two previous ones. It incorporates the three classical molecular mechanisms of (i) chemical DNA modifications, (ii) histone modifications, and (iii) the role of micro RNAs (Chen et al. 2016b; Tollefsbol 2017; Wang et al. 2017; Danchin et al. 2019a, b). It also incorporates all heritable processes of phenotypic variation usually ignored in this context, such as prions and chaperon molecules that constitute other forms of molecular memory (Halfmann and Lindquist 2010; Lindquist 2011; Halfmann et al. 2012; Saibil 2013; Manjrekar 2017; Newby et al. 2017), cytoplasmic inheritance (reviewed in Bonduriansky and Day 2018), parental effects (review in Danchin et al. 2011), ecological inheritance (Odling-Smee 1988, 2010; Odling-Smee et al. 2003; Odling-Smee and Laland 2011), cultural inheritance (van Schaik et al. 2003; Krutzen et al. 2005; Whiten et al. 2005; Whiten 2011, 2017; Whitehead 2017; Danchin et al. 2018), as well as the inheritance of the microbiota (Fellous et al. 2011).

This all-inclusive understanding encompasses all the processes that can produce intergenerationally persistent phenotypic variation, and thus parent–offspring resemblance. In this sense, it matches the classical view that epigenetics encompasses any process involved in heredity be it genetic or non-genetic. This understanding should stimulate the study of the role of epigenetic variation in medicine, ecology, and

evolution, as non-genetic inheritance and early in life effects are likely to affect strongly the fate of populations at all timescales. Bridging "infra-individual approaches" (molecular biology, development, physiology, neurobiology, to which the two previous understandings belong) with "supra-individual approaches" (behavior, demography, population genetics, ecology, and evolution) is in itself a big challenge. As a matter of fact, we need to acknowledge that there is an unnecessarily sharp border between these vast domains of biology (Danchin and Pocheville 2014; Pocheville and Danchin 2015), with the effect of forbidding any integration along the continuum from molecules to ecosystems. My goal is to make this border more permeable by unifying development and physiology with population dynamics in an ecological and evolutionary perspective to allow infra-individual studies to meet evolution (Danchin and Pocheville 2014; Pocheville and Danchin 2015). In this way, my hope is that it can help building bridges toward the Inclusive Evolutionary Synthesis, which I briefly describe in the next section.

1.5.3 We Need an Inclusive Rather than Only an Extended Evolutionary Synthesis

Adopting this fourth understanding of epigenetics can help going beyond the simple extension of the Modern Synthesis of Evolution (called the Extended Evolutionary Synthesis) that in effect only incorporates epigenetics in its developmental and evolutionary understandings (Pigliucci 2007, 2009; Pigliucci and Müller 2010; Danchin et al. 2011; Mesoudi et al. 2013; Laland et al. 2015; Muller 2017; Bonduriansky and Day 2018; Lu and Bourrat 2018), thus forbidding us from integrating all known mechanisms of inheritance into an "Inclusive Evolutionary Synthesis" (see Glossary; Danchin 2013; Cortez et al. 2017; Pocheville and Danchin 2017; Burunat 2019; Danchin et al. 2019a, b).

The inclusive understanding of epigenetics that I propose here, aims at connecting all fields of biology for a broader synthesis going beyond the sole sequencic component of inheritance to integrate all dimensions of heredity. All domains of biology are concerned as "Nothing in Biology Makes Sense Except in the Light of Evolution" (Dobzhansky 1973). Only such an integrative synthesis can allow us to understand and predict dynamical processes of interaction among individuals within populations, communities, and ecosystems at the ecological and evolutionary scales. I have qualified this ambitious new synthesis with the word Inclusive (Danchin and Wagner 2010; Danchin 2013; Danchin et al. 2011, 2019a, b) instead of Extended for the same reason as those that lead me to propose an inclusive definition of epigenetics. In effect, just adding one of the identified mechanisms of non-genetic inheritance (most likely epigenetics because of its molecular nature) would fully justify the word "extended," while the word "inclusive" would demand the inclusion of all known dimensions of inheritance. The expression Inclusive Evolutionary Synthesis thus flags that "all-inclusive" ambition in order to

incorporate all known processes of inheritance into the evolutionary theory of the twenty-first century. In other words, if we are to modernize the Modern Synthesis, we should do it thoroughly.

Finally, it is important to restate that, as Einstein did not invalidate Newton, the Inclusive Evolutionary Synthesis that we are currently building does not invalidate the current Modern Synthesis, but rather builds on it and broadens it in order to incorporate all processes of inheritance and hopefully all major characteristics of life into a unifying conception of biology.

1.6 A Practical Taxonomy of Epigenetics

I now propose a straightforward and easy to use classification of definitions that I suggest may help clarifying concepts of epigenetics for the various fields of biology in everyday research. With that goal, I purposely focus on the actual words of definitions, while ignoring the actual context in which the authors of these definitions worked. The resulting taxonomy is partly orthogonal and partly overlapping with the understandings developed above. This is a provocative approach revealing interesting discrepancies between the definition used and the actual goal of the approach of the corresponding research teams.

1.6.1 Principles of the Classification

Table 1.1 proposes a five-level classification only focusing on the current meaning of the terms of the definition itself and independently from the context in which each definition was produced and used. **Group D1** are developmental definitions that do not specify that the concerned phenotypic variation among cells is transmitted during mitosis. Such definitions thus incorporate transitory changes in gene expression that participate to everyday cell metabolism. **Group D2** are developmental definitions that incorporate the necessity that the epigenetic states are transmitted across cell generations (i.e., through mitosis). Groups D1 and D2 make a meta-group of developmental definitions, the latter being more complete. **Group A** encompasses definitions that are ambiguous because they do not specify whether the stability of epigenetic stages only concerns mitosis (in which case they would belong to the D2 category), or also implies a stability during the reproduction of multicellular organisms (in which case they would belong to group E). In Table 1.1, I underline the term (s) that is(are) ambiguous. **Group E** definitions add the criterion of stability of epigenetic marks across reproduction of multicellular organisms. This implies that epigenetic marks either can escape the waves of demethylation re-methylation occurring at meiosis and fertilization, or be reconstructed at every generation. I avoid the term "meiotic" because there are fascinating examples in which epigenetic information does not persist through meiosis but is added de novo later during

gamete maturation. For instance, the transmission of acquired diabetes (Type II diabetes) to offspring involves specific small non-coding RNAs injected into maturing sperm cells during their transfer through the epididymis (Chen et al. 2016a; Sharma et al. 2016). **Group I** correspond to the inclusive understanding of epigenetics proposed above. It is much broader than other definitions, and is particularly suited for ecologists to integrate all inclusively heritable causes of phenotypic variation be they genetic or not.

1.6.2 Applying this Taxonomy

Applying this logic to a sample of definitions highlights interesting discrepancies between the definition used and the ultimate goal of the corresponding studies (Table 1.1). All classifications have their pros and cons. To be efficient, however, a classification should be straightforward and minimize ambiguity. However, minimizing ambiguity often does not eliminate all ambiguities, as in the classification of Table 1.1, where ambiguities lie in the frequent use of the concept of heritability without specifying the time scale involved. The term heritability comes from evolutionary ecology and quantifies the statistical link between phenotypic similarity and the degree of kinship between pairs of individuals, usually measured as the coefficient of genetic relatedness. Nonetheless, the same term (as well as other terms such as inheritance, heredity, phenotypic stability, or perpetuation of variation) often qualifies cellular stability or memory, i.e. the fact that within a multicellular organism a cell of a given phenotype mitotically produces daughter cells of the same phenotype (Skinner 2011a). In itself, transposing the concept of heritability to cell lineages is not problematic when the term is qualified with a term such as "mitotically" or "meiotically" because this specifies the time scale of the concerned stability. However, using these terms without such qualifications makes them ambiguous (concerned definitions make a specific category in Table 1.1 where the ambiguous terms are underlined).

The discrepancies between the above historically driven parts and Table 1.1 stem from the fact when discussing the understandings above, I gave more weight to the scientific, conceptual, and historical context, while the classification reported in Table 1.1 is based only on the actual terms of the definition and nothing else. The resulting discrepancies suggest that scientists often adopt definitions that are not the most suitable for their specific approach, potentially generating some ambiguities. It is thus central for ecologists to adopt a definition of epigenetics that is adapted to their level of analysis, namely that of individuals within populations and ecosystems. I thus suggest that ecologists should use the inclusive definition of epigenetics proposed above.

1.6.3 Potential Applications

What can the above definitions of epigenetics bring to the different domains of biology? First, the fact that terms change significance according to the scientific domain is not problematic as long as the adopted definition is appropriate to the scientific questions. My goal here was to stress the plurality of concepts of epigenetics, in order to clarify their uses, hopefully leading scientists to use an appropriate definition in view of their specific approach.

Second, we all have engraved in our brains a sequencic vision of inheritance. We need to fight against this prejudice to integrate the multidimensionality of inclusively heritable sources of variation beyond and in interaction with sequencic. In other words, after observing that a trait is heritable, we should not limit ourselves to the sole exploration of DNA sequence variation and explore other inclusively heritable sources of parent–offspring resemblance.

Third, adopting an inclusive understanding of epigenetics would help avoiding that the new evolutionary synthesis gets trapped into a purely molecular vision of inheritance, hence ignoring important processes such as cultural inheritance that can affect many behavioral and non-behavioral traits, such as obesity and diabetes (Avital and Jablonka 2000; Danchin et al. 2019a, b). In effect, inheritance also implies mechanisms, such as cultural inheritance (a major form of early in life effects) that mainly involves learning, a process that emerges at the scale of the brain rather than at the sole molecular level. This statement is true, despite the fact that it is highly likely that a high proportion of non-genetic processes of inheritance have some kind of epigenetic basis (Danchin et al. 2019b), as this is the case, for instance, of learning (Miller and Sweatt 2007).

Fourth, accepting the inclusive understanding of epigenetics has many consequences for the study of early in life effects, as some of them become inclusively heritable after their acquisition before reproduction (among others see the many examples reviewed in Wang et al. 2017; Danchin et al. 2019b). When early in life effects produce parent–offspring resemblance, the risk is high that they are considered as genetic, because most of the time we do not witness the initial stress that initiated the effect and triggered inclusively heritable variation, which can only be of a non-sequencic nature, probably often implying some variation in epigenetic states. Qualifying them of genetic origin may trap generations of researchers into purely sequencic studies. For instance, we now know that the strong heritability of ill-parental behavior in mammals including humans is due to the fact that the mothers' behavior constitutes a component of their pups' environment that triggers the emergence of epigenetic marks leading their daughters to reconstruct the same ill-parental behavior when adults (Denenberg and Whimbey 1963; Francis et al. 1999; Champagne 2008, 2020; Curley et al. 2008). More generally, parents in any species providing parental care constitute a major early in life component of their offspring environment affecting their epigenetic marks and interacting with other types of information carried out by the germline in shaping the phenotype in a heritable way (Champagne 2020). This reasoning can be generalized to any species

as even parents of species without parental care can shape their offspring phenotype through non-sequencic information in their gamete. Such parental effects can be viewed as very early in life effects. This poses that plastic responses to environmental changes can be transmitted to offspring through pathways involving early in life effects for at least several generations, in a way that can perfectly mimic genetic transmission when tested over a single or even a few generations (Danchin 2013). The knowledge about the mechanisms underlying these effects opens fantastic research avenue to define therapies to cure such ill behavior in order to stop the vicious circle generated by this form of epigenetic inheritance in humans.

Fifth, similarly, the inclusive understanding of epigenetics has many consequences for the study of adaptation. For instance, transposons that strongly interact with epigenetics can participate to adaptation by translating phenotypic adaptation into genetic variability, in a form of genetic assimilation (Rey et al. 2016; see also Danchin et al. 2019b; Pimpinelli and Piacentini 2020). Furthermore, all in all the non-genetic part of inclusively heritable information vastly expands the range of the sources of heritable variation (e.g., genetic, epigenetic, cultural, ecological, microbiota, prions etc.) on which selection can act. It implies that many of the adaptations we observe in nature may be inherited at least partly through other bearers than the DNA sequence, one of which being epigenetics in its evolutionary understanding. Furthermore, the fact that the various inheritance systems are suspected to influence each other (Danchin et al. 2019b) makes an inclusive approach even more necessary, and adopting such an approach represents a considerable paradigm change for ecologists in particular because it fully changes the potential bearers of adaptation, which is at the heart of all eco-evolutionary approaches.

Sixth, such mechanisms can strongly affect the design of conservation actions in the context of global change with its series of directional environmental changes (e.g., steadily increasing temperature). For instance, epigenetic variation in itself should be considered as a component of biodiversity in a way that is similar to sequencic variation (Rey et al. 2020). The same holds for cultural variation. Several authors have recently argued that we should also account for cultural variation in conservation that is made inclusively heritable by social learning (Brakes et al. 2019). For instance, after reintroduction into a habitat that remained unoccupied for years, migratory ungulates took quite some time to rediscover migration routes and wintering grounds (Jesmer et al. 2018). This implies that the loss of ancient cultural knowledge adds further threats of extinction during the initial phase of reintroduction when organisms build a new knowledge about their environment. In other words, we should integrate all the dimensions of inclusive epigenetics into conservation in order to protect natural populations properly.

To sum up, the inclusive understanding of epigenetics teaches us that the variation underlying many heritable traits (which are called genetic traits for that sole reason) might be of a non-sequencic nature. This is particularly true for all inherited early in life effects. Furthermore, the existence of epigenetically mediated inheritance often involving early in life effects probably considerably increases the adaptive capacities of populations to global change. The fact that epigenetic states

constitute a hub in most if not all plastic responses (Danchin et al. 2019b), and that some of these epigenetic states can be transmitted across generations may reinforce adaptive virtuous circles or extinction vortexes.

1.7 Conclusions

The large variety of understandings of epigenetics stems from the fact that epigenetic processes are ubiquitous in all aspects of living organisms, a high proportion of them involving some kind of early in life effects. Therefore, it is necessary to adopt a definition of epigenetics that is relevant to the type of research question. To fit within this philosophy, here I propose and recommend the use of an inclusive understanding of epigenetics that is particularly relevant to medical, ecological, and evolutionary studies, in part because that understanding can naturally encapsulate all types of early in life effects. Furthermore, this broader vision of epigenetics is likely to help bridging concepts of epigenetics at the infra-individual biology with those of supra-individual biology including behavioral, populational, functional, and evolutionary ecology, as well as medicine. To me, the merging, or full integration, of all sub-disciplines of biology into an inclusive biology studying all processes within a continuum from molecules to ecosystems constitutes the current major ambition for biology. The implementation of such an Inclusive Evolutionary Synthesis that I advocate here will occur only if members of all disciplines of biology are able to listen to and respect the approaches of the other disciplines, which often proves to be difficult. Furthermore, the adoption of this broader vision of life is likely to greatly help understanding and predicting the consequences of climate change at the various scales of individual accommodation, population dynamics and adaptation, food webs, ecosystem and biodiversity dynamics. I am convinced that only such an inclusive theoretical framework incorporating all available knowledge at all scales of living systems, from molecular to ecological interactions can allow us to achieve such an ambitious and demanding goal for the future of humanity on planet Earth.

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Glossary

Extended Evolutionary Synthesis A trend in evolutionary science, that took momentum at the turn of the twenty-first century and that puts more emphasis

on the role of development, environmental factors, as well as some non-genetic forms of inheritance in the evolutionary processes (mainly if not exclusively epigenetics in its developmental and evolutionary understandings: Pennisi 2008; Pigliucci and Müller 2010; Laland et al. 2015; Lu and Bourrat 2017).

Genetic Here, I use this term in its most common modern sense of sequencic, i.e. information encoded in the DNA sequence of nucleotides. Note that this meaning is highly reductionist relative to the initial meaning that encompassed everything that participates to heredity.

Genetic assimilation A process by which a phenotype initially induced by a specific environmental factor, becomes genetically determined through selection. Note that, at the time of Waddington, the term genetic meant anything that is inherited. In particular, Waddington's experiments did not show that the initially plastic trait became encoded into the DNA sequence, but rather, that it lost its plasticity and became inclusively heritable (Danchin et al. 2019b).

Heredity Patterns of parent–offspring resemblance. It is widely accepted in biology that heredity results from parents transmitting information to their offspring, though the nature of this information is still at the heart of a hot debate (e.g., Sarkar 1996; Godfrey-Smith 2000; Maynard Smith 2000; Pocheville 2018; Danchin et al. 2019b).

Heritability Usually, this term quantifies the part of phenotypic variation that is inherited genetically, either additively (narrow sense heritability) or total (broad sense heritability). It is measured at the level of a population. It quantifies parent–offspring resemblance at play in quantitative genetics. Today heritability is usually associated to variation in DNA nucleotidic sequence alone (Danchin and Wagner 2010; Danchin et al. 2011). For more details, see (Bourrat 2015). In Table 1.1, I also point at the transposition of this term to depict the persistence of cell characteristics along cell lineages of multicellular organisms.

Inclusive Evolutionary Synthesis The evolutionary synthesis ambitioning to incorporate *all known dimensions of inheritance* into a single theoretical framework. It incorporates the inclusive understanding of epigenetics that I develop here.

Inclusive heritability Statistical term quantifying the degree of parent–offspring resemblance, *whatever the mechanisms responsible for it* (whether sequencic or not, Danchin and Wagner 2010; Danchin et al. 2011). It is the heredity of difference, whatever the underlying mechanism. Often in this book chapter, I use the term heritability in the meaning of inclusive heritability, because historically it was the initial meaning of this term. Inclusive heritability is the corner stone of evolution through natural selection and drift.

Infra-individual processes Biological processes occurring within an organism during its lifetime, including gene expression, cell functioning, physiology, neurobiology, as opposed to supra-individual processes. Corresponds to what Mayr (1961) called functional biology.

Inheritance The set of mechanisms producing parent–offspring resemblance.

Intergenerational epigenetic inheritance The set of epigenetic mechanisms that produce resemblance between two successive generations.

Modern Synthesis (of evolution) A trend in evolution, first coined by Julian Huxley in 1942, that brought together Darwinism, Mendelism, and population genetics in order to provide a powerful account of the mechanisms of evolution. Also called Neo-Darwinism although these two terms often cover different approaches. In this trend, the focus is mainly on genes (today understood as sequencic). A purpose of the extended or inclusive syntheses is to extend it beyond the gene.

Non-genetic inheritance Mechanisms of inclusively heritable variation that do not result from variation in the DNA sequence (Danchin and Wagner 2010; Danchin et al. 2011). Equivalent to non-sequencic inheritance.

Sequencic Term that was first casually used by Hervé Philippe in a discussion to depict the pervasive trend among biologists and the grand public to reduce inherited information to the sole information encoded into the DNA sequence of nucleotides. It can replace the term genocentrism that I used before that is ambiguous because of the many understandings of all the terms of the "gene" family (genetics, genomics. . .).

Supra-individual processes Interactions occurring among individuals within populations, communities, and ecosystems. These integrate transgenerational processes such as heredity. This is the domain of ecology and evolution. Corresponds to what Mayr (1961) called evolutionary biology.

Transgenerational epigenetic inheritance The set of epigenetic mechanisms that produces resemblance across multiple ($\geq$2) generations of organisms.

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Chapter 2
For Better or Worse: Benefits and Costs of Transgenerational Plasticity and the Transhormesis Hypothesis

David Costantini

Abstract Adaptive transgenerational effects are not easily explainable with stringent principles of genetic inheritance. For example, in environments that change rapidly, selection of given genotypes in one generation may be too slow to occur as in species with long generation times. Organisms can respond phenotypically to such changes. Phenotypic plasticity is one mechanism through which organisms rapidly respond and maintain reproductive fitness under variable conditions. This type of environmentally-induced phenotypic variation transmitted across generations is called transgenerational plasticity. In this book chapter, I discuss the key theoretical and mechanistic aspects that make a biological process called hormesis one relevant source of transgenerational plasticity. To this end, I propose the *transhormesis hypothesis*, whereby hormetic priming of the parents is transmitted to their offspring so that they are better prepared to withstand future challenges. I discuss the transhormesis hypothesis in the framework of environmental toxicology to highlight the role of transhormesis in favouring adaptability or adaptation of species to environmental changes in the Anthropocene. Finally, I critically appraise our current knowledge of environmental hormesis, highlighting key future directions for the field.

2.1 Introduction

Heredity lies in our genes. This almost dogmatic idea is one pillar of modern evolutionary theory. Genetic adaptation (change in gene frequencies across generations) is a fundamental mechanism of biological evolution that enables organisms to respond to gradual environmental changes, that occur over many generations, so that they adjust their phenotype to the prevailing environmental conditions. This gene-centred view of evolution does not, however, explain inheritance in all its complexity (Danchin et al. 2019). The genetic information is very stable, with low

D. Costantini (✉)
Unité Physiologie Moléculaire et Adaptation, UMR 7221, Muséum National d'Histoire Naturelle, CNRS, CP32, Paris, France

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estimated rates of change (Ness et al. 2012; Ségurel et al. 2014). This stability constrains adaptability under several contexts. For example, in fast changing environments, genetic selection in one generation may be either maladaptive in the next generation or too slow to occur as in species with long generation times. Organisms can, however, respond phenotypically to such changes, and the new phenotype may later become genetically encoded by natural selection (genetic assimilation). These transgenerational effects are not easily explainable with stringent principles of genetic inheritance, rather they would invoke the co-participation of Lamarckian mechanisms in shaping phenotypes (Danchin et al. 2019).

Phenotypic plasticity is one main source of phenotypic evolution. It refers to the ability of a single genotype to express different phenotypes in response to variability in environmental circumstances (Beaman et al. 2016). Phenotypic plasticity refers to all sorts of environmentally-induced phenotypic variation, which can be reversible or irreversible, adaptive or maladaptive, active or passive, and continuously or discontinuously variable (Stearns 1992; West-Eberhard 2003). We can recognize two broad categories of within-generation phenotypic plasticity: *developmental plasticity* induced by the pre- and/or post-natal environmental conditions that organisms experience, and *reversible plasticity* that occurs within reproductively mature organisms. These types of phenotypic plasticity are not necessarily mutually exclusive. They are probably linked, possibly to provide a 'fail-safe' to counteract the maladaptive effects of one type of plasticity. Beaman et al. (2016) suggested that acclimation (one type of reversible plasticity) might reduce the costs of developmental plasticity, when there is a mismatch between environmental conditions experienced during development and in adulthood. The advantage of the interaction between developmental plasticity and acclimation would lie in matching phenotypes not only to mean environmental conditions, but also to their potential for change (at least within given limits of magnitude and rapidity).

Plasticity is not expressed only within a single generation. It can actually be transmitted by parents to offspring. This type of environmentally-induced phenotypic variation transmitted across generations is called *transgenerational plasticity*. To date, its mechanistic aspects, long-term stability, and potential fitness benefits and costs remain largely ununderstood. In this book chapter, I discuss the key theoretical and mechanistic aspects that make a biological process called *hormesis* one relevant source of transgenerational plasticity. To this end, I propose the *transhormesis hypothesis* and put it in the framework of environmental toxicology to highlight the role of transhormesis in favouring adaptability or adaptation of species to environmental changes in the Anthropocene. Finally, I critically appraise our current knowledge of environmental hormesis, highlighting key future directions for the field.

2.2 Transgenerational Plasticity

Transgenerational plasticity occurs when the environment experienced by a parent influences the development, the adult phenotype, and/or the fitness of their offspring. A simplified conceptual framework to illustrate how transgenerational plasticity is transmitted across generations is as follows: parents (F0) experience a certain number of environmental stimuli, decode them, and pass cues to their offspring (F1) either directly by parental care or through the egg, the spermatozoon, or the placenta. F1 offspring merge parental cues with those they experience themselves from the environment in order to orchestrate their development. Thus, F1 offspring may pass a combination of cues to the next generation (F2) later in life. In other words, F2 offspring might receive cues by both F0 and F1. A number of factors will determine whether transgenerational information will be advantageous. For example, parental experience early in life might be relevant for their offspring if there is a certain degree of matching between their development environment and that of their offspring (environmental autocorrelation, Frankenhuis et al. 2019). Also, the temporal window during which offspring receive the cue is very important (Fawcett and Frankenhuis 2015); cues received earlier in development appear to have a stronger phenotypic effect than those received later in development (e.g., *epiphenotype hypothesis*, DeWitt et al. 1998; Bell and Hellmann 2019).

Whether the experiences of one generation can influence the fitness of future generations is a controversial topic. A main question is whether such effects are important for long-term evolutionary processes because they might be transient and washed away within a generation. Bell and Hellmann (2019) identify a number of potential multigenerational outcomes of a cue experienced by the F0 generation; for example, effects may persist for more than one generation or do not persist until F2, bouncing back to the original phenotype. Even if a phenotype is not expressed, this does not necessarily mean that the transgenerational information faded out. It might still be present in a given generation (e.g., silent carriers of epigenetic information; Bell and Hellmann 2019), but it will be expressed only in the next one.

Transgenerational plasticity can be maladaptive under a scenario of environmental mismatch. For example, if parents experience a novel stressor that offspring will not experience, the cue they will transmit might induce phenotypic adjustments that will be costly to maintain in absence of that particular stressor. Although the environmental mismatch paradigm is plausible in all-or-nothing scenarios (e.g., presence or absence of a toxicant), it does not make clear predictions for circumstances where a stressor can occur at different intensities along a linear gradient (e.g., stress level). Here I make the point that the hormesis paradigm would foster our capacity to explain certain types of transgenerational outcomes (*transhormesis hypothesis*).

2.3 Hormesis

The term hormesis, coined for the first time by Chester Southam and John Ehrlich (1943), is currently used in at least three different ways. The first relates to its original use in describing a situation in which the response to an environmental stressor is biphasic, with low intensities eliciting a stimulatory or beneficial response, and high intensities causing inhibition or toxicity (Costantini et al. 2010; Mattson and Calabrese 2010). For example, growth and biomass of *Solanum melongena* were increased by exposure to low concentrations of cadmium, but were inhibited at higher cadmium concentrations (Siddhu et al. 2008). Fecundity of spined soldier bugs *Podisus maculiventris* was increased by acute exposure to low concentrations of the pesticide imidacloprid as compared to controls or to bugs exposed to high concentrations (Rix and Cutler 2020).

The second use of the term hormesis is the priming or conditioning effect, whereby exposure to a low level of a stressor results in the organism being better able to cope with exposure to that stressor (or, potentially, to a different one) when encountered on subsequent occasions (Calabrese et al. 2007; Costantini et al. 2010, 2012, 2014). For example, hormetic priming to some types of pesticides can increase tolerance later in life or increase expression of life-history traits, such as number of offspring generated or longevity (Suwanchaichinda and Brattsten 2001, 2002; Boyer et al. 2006; Poupardin et al. 2008; Rix and Cutler 2018).

A third emerging use of the term hormesis relates to a prolonged exposure of the organism to a given stressor that elicits a stimulatory or beneficial response only if the dose of such stressor is moderate. For example, continuous exposure to low concentrations of imidacloprid increased fecundity of green peach aphids (*Myzus persicae*) as compared to controls or to aphids exposed to high concentrations (Ayyanath et al. 2013). This type of hormesis needs to be distinguished from acclimation, which, conversely from hormesis, is a reversible process, i.e., the organism's status bounces back to that expressed prior to exposure to the environmental stimulus.

In recent times, there has been growing interest in understanding whether any effects of hormetic priming carry over to the next generations and, if yes, which circumstances favour transgenerational hormesis. In the following paragraph, I discuss studies that provide evidence for the idea that I refer to as the *transhormesis hypothesis*.

2.4 The Transhormesis Hypothesis

Exposure to an environmental stressor is not an all-or-nothing scenario because stressors occur in different intensities. Thus, it might not be correct to estimate pros and cons of exposure to a low-intensity stressor by extrapolation of the data from exposure to the same but, high-intensity, stressor. For example, conditioning or

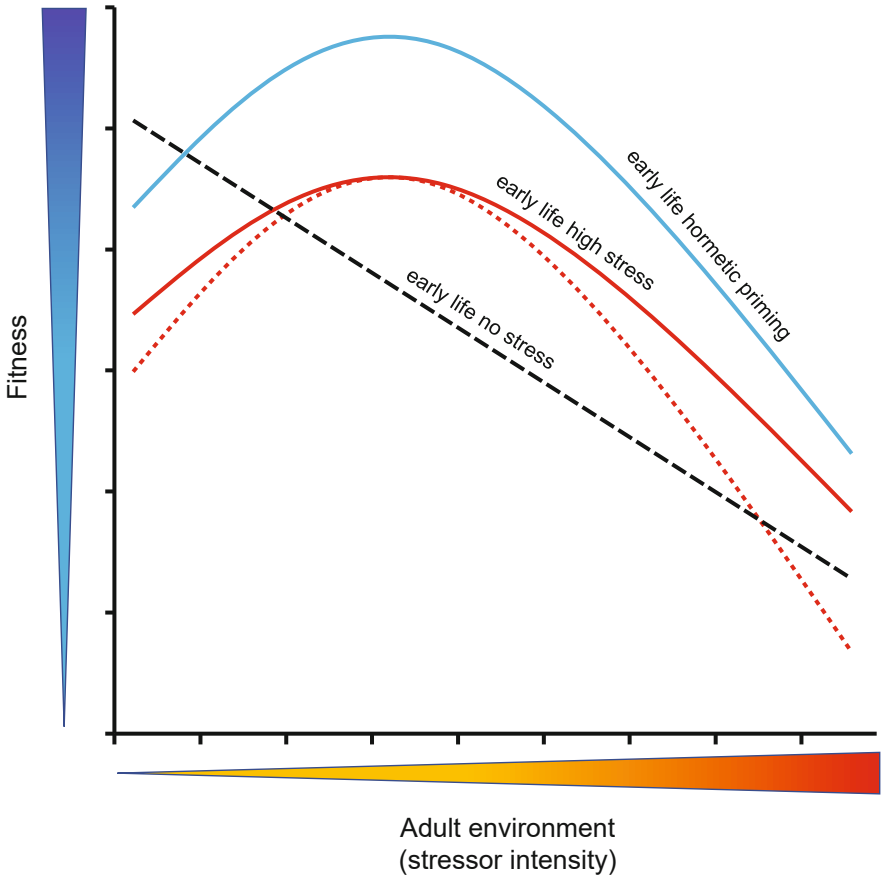

Fig. 2.1 The potential effects of exposure to a stressor during development on subsequent Darwinian fitness. The solid lines show the fitness consequences when various levels of the stressor are encountered in adulthood for individuals that previously encountered moderate (solid blue line, hormetic priming) or high (solid red line) intensity of the same stressor earlier in life (this early life pre-exposure is not shown). The hormetic priming during development will increase fitness at all levels of subsequent exposure, but, as compared to individuals that did not experience any stress early in life (dashed black line), will carry a cost if the stressor is not subsequently encountered or encountered at a very low level. Early life high stress will have costs for fitness at all levels of subsequent exposure as compared to hormetic priming and to low (solid red line) or even high (dashed red line) levels of subsequent exposure as compared to individuals that did not experience any stress early in life (dashed black line)

priming of stress responses early in life may induce (almost) irreversible phenotypic adjustments that may carry fitness benefits providing the stressor is then encountered in the adult environment (Fig. 2.1). There might be a cost of phenotypic adjustment if there is no subsequent exposure to that stressor in adulthood. This may occur when the early life environment does not match the conditions experienced in adulthood (Costantini et al. 2014). Hormetic conditioning may also occur in adulthood, but the

stimulatory effects are of smaller magnitude as compared to those induced by conditioning during sensitive windows of development (Mattson and Calabrese 2010).

Here I propose the transhormesis hypothesis, whereby hormetic priming of the parents is transmitted to their offspring so that they are better prepared to withstand future challenges. This hypothesis contrasts the widespread all-or-nothing scenarios, which do not take into account the continuous nature of stressors nor the importance of their intensity. A growing number of studies are providing evidence for transgenerational hormetic effects. The benefits of an acquired phenotypic resistance or tolerance and its transmission across several generations were observed in a number of systems, including exposure to heat stress (Whittle et al. 2009; called transgenerational acclimation by the authors, Donelson et al. 2012), pesticides (Ayyanath et al. 2013; Rix and Cutler 2018), ionizing radiation (Byrne et al. 2014), or other stressors (Kishimoto et al. 2017). In the following paragraph, I discuss the role of transhormesis in environmental toxicology.

2.5 Transhormesis in the Context of Environmental Toxicology

There is ample evidence to suggest that exposure to low doses of some toxicants, such as pesticides (including DDT), metals, or ionic liquids, may induce hormetic effects (e.g., Heinz et al. 2012; Cutler 2013; Liu et al. 2020; Yu et al. 2020). One of the earliest papers was that of Sun (1945), who observed that bean aphids (*Aphis rumicis*) exposed to low concentrations of rotenone produced more offspring than control aphids or than aphids exposed to high concentrations. The question then is whether such hormetic effects are limited to one generation or carry over to next generations.

Surges in population size growth of several insect species at rates higher than expected were observed many times following pesticide usage (e.g., Chelliah and Heinrichs 1980; Morse and Zareh 1991). Selection of resistant genotypes is one important evolutionary mechanism through which insects become resistant to a certain pesticide (Hawkins et al. 2019). We have, however, evidence that acquisition of phenotypic resistance is also important. Within this context, hormesis might play an important role because breakdown of pesticides in agricultural fields can expose organisms to low concentrations of these chemicals during sensitive windows of their life cycle. Several experimental studies found that exposure of parents to low sublethal concentrations of certain types of pesticides may increase resistance of next generations.

Ayyanath et al. (2013) found that continuous exposure to sublethal concentrations of the insecticide imidacloprid (class of neonicotinoids) induced transgenerational hormesis in the green peach aphid, *Myzus persicae*. After four generations, aphids exposed to low concentrations of imidacloprid had higher

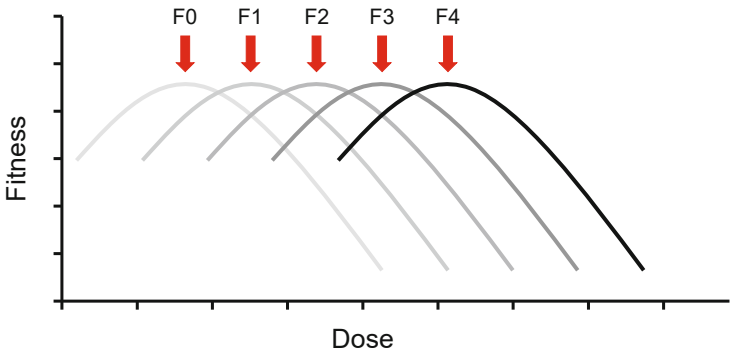

Fig. 2.2 The peak hormetic concentration or magnitude of a given pollutant or other environmental stressor may shift across generations, indicating potential of the hormetic zone (stimulatory area under the curve) to evolve

fecundity compared to control aphids or to those exposed to higher concentrations. The results of this experiment also provided two additional relevant patterns. Intermediate generations had lower fecundity (Ayyanath et al. 2013), indicating a potential fitness cost of transhormesis that was later compensated by subsequent generations. There was also a shift to a higher peak hormetic concentration from F0 to F1 (Ayyanath et al. 2013), indicating that the hormetic zone might evolve across generations (Fig. 2.2).

The occurrence of transgenerational trade-offs has also been observed in other study systems. For example, Chen et al. (2020) found that nymphs of the brown citrus aphid (*Toxoptera citricida*) exposed to a sublethal concentration of imidacloprid had a development duration slightly longer than controls, but also a better survival and fecundity (Chen et al. 2020).

Transhormesis can also foster cross-resistance. For example, hormetic priming to imidacloprid could increase survival of aphids when being later exposed to a combination of food and of water stress (Rix et al. 2016). However, this is not a general pattern. Rix and Cutler (2018) show that exposure of aphids to a hormetic concentration of imidacloprid reduced mortality of their offspring exposed to higher concentrations of imidacloprid after multiple generations of exposure. However, the hormetic concentration of imidacloprid did not prime offspring to better resist exposure to spirotetramat, which is an insecticide with a different mode of action. Similarly, embryonic exposure of wood frogs to carbaryl (AChE-inhibitor) increased resistance to carbaryl itself, malathion (AChE-inhibitor), and cypermethrin (Na^+ channel interferer), but not to chlorpyrifos (AChE-inhibitor) or to permethrin (Na^+ channel interferer; Hua et al. 2014a; see also Hua et al. 2013). These results demonstrate that pesticides may induce cross-tolerance that is not restricted to pesticides with the same mode of action, but it is unclear why cross-tolerance does not always occur.

Evidence for hormesis induced by pesticides has also been found in plants (Cedergreen 2008; Brito et al. 2017). For example, Belz (2020) found that exposure

of PSII target-site resistant plants of *Chenopodium album* to the herbicide metamitron stimulated their reproduction and increased tolerance of their offspring to metamitron

Duration of exposure to pesticides might be important in determining a role of hormetic priming in fostering tolerance. Where exposure early in life to a given pesticide is prolonged, selection might favour constitutive expression of traits that come at a cost for plasticity (induced tolerance). Thus, protective traits are kept upregulated to some degree. This scenario is suggested by an experiment on wood frogs (*Lithobates sylvaticus*) located close to or far from agricultural fields: exposure of amphibian embryos and hatchlings to sublethal concentrations of the insecticide carbaryl increased tolerance later in life only in individuals from populations that were far (and thus less exposed to it) from agricultural fields (Hua et al. 2014b).

Examples of transhormesis have also been observed for other pollutants. For example, Kishimoto et al. (2017) found that F1 descendants from *Caenorhabditis elegans* parents stressed with arsenite showed enhanced resistance to oxidative stress compared with those from control parents. These beneficial effects were also evident in the F2 generation, but they gradually declined and almost disappeared in F3 generations. Transhormesis is not limited to pollutants, but it also applies to other relevant human-induced effects on the environment. For example, offspring of parents exposed to high pCO_2 had greater settlement and survivorship immediately following release, retained survivorship benefits during 1 and 6 months of continued exposure, and further displayed growth benefits to at least 1-month post release (Putnam et al. 2020).

The question then is which conditions make hormesis ecologically and evolutionary possible. In the following paragraph, I discuss a recent modelling paper that illustrates some of the key attributes of transhormesis.

2.6 Modelling Transhormesis

Simulation models allow to formalize concepts, and to define the most essential aspects of a given process/mechanism. Costantini and Borremans (2019) proposed some mathematical simulations to establish the hypothetical conditions that make priming (or conditioning) hormesis ecologically and evolutionary possible. In particular, as main attributes, they identified the (i) degree of stress predictability during early and late life stages (stress match probability), (ii) role of hormesis potential of given genetic variants, and (iii) impact of trade-offs between the benefits and costs of having hormesis potential on the reproductive fitness.

The simulations suggest that, in most situations, the benefits of individuals with hormesis potential emerge if stress conditions do not change too often. In other words, if there is a low probability that stress conditions remain the same, the benefits of early life priming never exceed the costs of stress (even for high benefit values) for individuals with a (epi)genetic variant that promotes hormesis (Fig. 2.3). Having hormesis potential and maintaining the functions associated with it (e.g.,

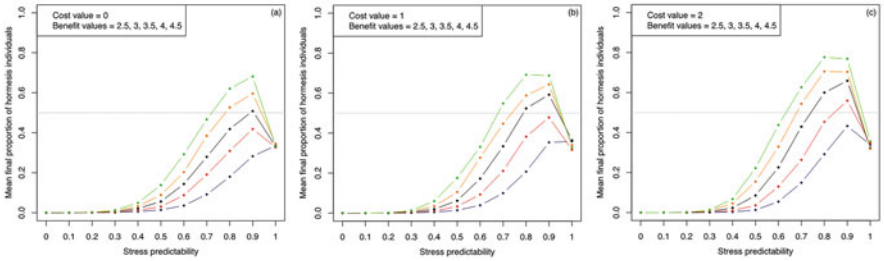

Fig. 2.3 Mean final proportion of individuals with hormetic potential in the population for a range of stress match probabilities, under different combinations of mild stress cost values during youth and hormetic potential benefit values in the case of mild youth stress followed by adult stress. Benefit values shown in decreasing order from top (green line) to bottom (blue line). The horizontal line indicates the transition where the reproductive fitness of individuals with hormetic potential is higher than that of individuals with no hormetic potential. Models include 30 generations, and the proportion of individuals with hormetic potential in the population at the end of the 30th generation is used as a proxy for their reproductive fitness (i.e. evolutionary success). Reproduced from Costantini and Borremans (2019)

resources required to maintain a molecular 'memory') are therefore costly for the individual if hormesis is not being expressed owing to a strong environmental mismatch. This cost would explain why natural selection favours system designs that require hormetic priming in order to work effectively.

The main attributes identified by Costantini and Borremans (2019) that are relevant for the evolution and maintenance of hormesis are supported by literature. For example, Rodriguez et al. (2012) show that there are genetic variants with stronger hormesis potential for heat stress, and Costantini et al. (2014) show that hormetic priming to heat stress may be costly under mismatch between early in life and adult environmental conditions (i.e., low degree of stress predictability). However, there is need of well-defined experiments that, relying on these theoretical considerations, validate or refine these models using empirical data about transgenerational effects of toxicants or of other environmental stressors.

2.7 Perspectives and Future Directions

In this chapter, I have encouraged careful consideration of hormesis in promoting transgenerational effects to advance the discipline theoretically and experimentally. In the context of environmental toxicology, it is unclear yet whether any hormetic priming (or conditioning) effect is restricted to the conditioning toxicant, if any effects become stronger under multigenerational exposure, or if toxicant-resistant states remain without renewed exposure to the agent. Also, for those studies that test a prolonged exposure to a hormetic dose, it is important to tease apart effects of hormesis from those of acclimation. One way to distinguish hormesis from acclimation is to look at reversibility of trait expression: hormesis induces (almost)

irreversible traits, while traits expressed under acclimation would change rapidly when the environmental conditions also change.

We should not lose sight of the complexity of a phenotype. Traits differ in capacity for plasticity or acclimation; traits can be fixed (skeletal size, but not in all taxa) or dynamic. Thus, traits might differ in their transgenerational pattern if their hormetic response differs, e.g., if it is induced at different doses of the agent or at different time windows of development. Also, we need to pay special attention to the synergistic and antagonistic effects owing to exposure to multiple anthropogenic stressors.

It is important to consider the within and among-species variation in life-history trajectories. Multigenerational hormetic treatment may result in a more heterogeneous population if offspring differ in their response (e.g., tolerance) to a same concentration of a given toxicant (Belz and Sinkkonen 2016; Rix and Cutler 2018). For example, effects of six toxicants (IAA, parthenin, HHCB, 4-tert-octylphenol, glyphosate, and pelargonic acid) among fast-growing individuals of *Lactuca sativa* usually started at higher doses compared to the population mean, while the opposite was found among slow-growing individuals (Belz et al. 2018). Very low toxin exposures tended to homogenize plant populations due to selective effects, while higher, but still hormetic doses tended to heterogenize plant populations (Belz et al. 2018). In other words, transhormesis may increase or reduce variation in body size of a given population within the limitations imposed by the costs of allocating resources to growth. This transhormetic effect on body size can have several ecological consequences because body size may affect a number of fitness-related traits, such as competition, nutritional needs, reproduction, and survival. Thus, transhormesis has strong potential to affect life-history trajectories.

Transhormesis might also play a relevant role in competition among species, e.g., when one species develops a stronger hormetic-induced tolerance to a given stressor than another one with which shares a similar ecological niche. For example, when exposed for seven generations to the insecticide nitenpyram, silverleaf whitefly (*Bemisia tabaci*) developed six-fold resistance to nitenpyram, and 3.1- and five-fold cross-resistance to imidacloprid and acetamiprid, respectively; by contrast, glasshouse whitefly (*Trialeurodes vaporariorum*) developed lower resistance to the nitenpyram and very low cross-resistance to imidacloprid (Liang et al. 2012). The higher adaptable nature of the silverleaf whitefly, when exposed to low doses of insecticides, might provide a selective advantage in the competition with glasshouse whitefly for exploiting crops.

We also know little about how effects of early in life environmental stimuli interact with parental age in determining resilience of offspring to later life stress exposure. Parental age is very important because work done on organisms ranging from invertebrates to vertebrates showed that offspring produced by older parents may show some degree of impairment in body function (Fox and Dingle 1994; Tarín et al. 2005; Bouwhuis et al. 2010; Rodríguez-Graña et al. 2010). It might be insightful to test whether the effect of early life priming offsets any detrimental effects of parental age on the offspring.

Finally, when we look at stability of the environment across generations, it is important to consider the longevity of animals because this trait is linked to the generation time and to the trade-off in the allocation of resources between somatic and germline functions.

2.8 Conclusions

There is now growing evidence that hormetic priming might play a significant role in driving transgenerational effects and adaptability of organisms to stressful circumstances. However, we have yet to clarify the extent to which transhormesis can last and have fitness consequences under different circumstances (e.g., different exposure scenarios in terms of types of toxicants and concentrations), and for co-specific populations and species. These issues could be addressed by the types of experimental setting outlined here and by prior work (Costantini and Borremans 2019) that would make the transhormesis hypothesis testable.

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Chapter 3
Adaptive Meaning of Early Life Experience in Species that Go Through Metamorphosis

Takashi Koyama, Catarina Nunes, Hesper Khong, and Yuichiro Suzuki

Abstract Many animals have complex life cycles in which juvenile and adult stages are separated by metamorphosis. Metamorphosis is a time of reprogramming, and early experiences can impact this reprogramming phase in many ways that are adaptive. Here we review the ways in which various insect species adjust the timing of metamorphosis and the morphogenetic processes during metamorphosis depending on their environment during the juvenile stage. Specifically, we focus on the various intrinsic and extrinsic cues that impact the growth of the whole body and individual body parts and provide examples of seasonal polyphenisms. We discuss the adaptive significance of these plastic responses to the environment and summarize our current understanding of the endocrine basis of developmental plasticity. We show that life history modularity and developmental modularity both facilitate integration of early environmental cues in the development of adult phenotypes.

3.1 Overview

3.1.1 Introduction

Many animals have complex life cycles where the juvenile and adult stages display distinct phenotypes. In these organisms, the juvenile and adult stages are typically separated by the process of metamorphosis, which is characterized by dramatic changes in morphology, behavior, and physiology. Metamorphosis is a successful

T. Koyama
Section for Cell and Neurobiology, Department of Biology, University of Copenhagen, Copenhagen, Denmark

C. Nunes
Instituto Gulbenkian de Ciência, Oeiras, Portugal

H. Khong · Y. Suzuki (✉)
Department of Biological Sciences, Wellesley College, Wellesley, MA, USA
e-mail: ysuzuki@wellesley.edu

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life history strategy that has evolved independently multiple times within the animal kingdom, including marine invertebrates, fishes, amphibians, and insects. By allowing juvenile and adult stages to exploit different habitats and/or food resources, metamorphosis enables each species to fine-tune the juvenile and adult development and physiology to maximize survival and fitness (Moran 1994).

Most aquatic species undergo metamorphosis, where juveniles hatch as swimming larvae, undergo metamorphosis, and transform into adults with distinct morphologies (Hadfield 2000). In many cases, the larval stage of these marine species is adapted for dispersal. Once the larvae find appropriate substrates, they settle and undergo metamorphosis (Fusetani 2004; Swanson et al. 2004; Lau et al. 2005; Whalan et al. 2015). The adults typically occupy the benthic environment, assisted by traits that allow them to adapt to this new habitat. Particularly dramatic changes in morphology and behavior are seen among the aquatic invertebrate species, such as cnidarians, mollusks, annelids, crustaceans, echinoderms, and tunicates, where a freely swimming larva eventually settles to become a more sessile—or in some cases, a completely sessile—adult. Aquatic vertebrate species, such as fishes and amphibians, also undergo metamorphosis. In the case of amphibians, metamorphosis can involve a transition from the aquatic to the terrestrial habitat with dramatic changes in both morphology and physiology that allow them to adapt to life on land (Brown and Cai 2007). Among terrestrial animals, perhaps the most striking and dramatic transformations are observed in insects.

At the cellular level, metamorphosis involves dramatic increase in cell proliferation, cell death, and tissue morphogenesis. Some species, such as echinoderms, take metamorphosis to the extreme where most of the larval tissues are replaced by new tissues that originate from a small rudiment within the larva (Chino et al. 1994). Similarly, in fruit flies, the entire adult body wall and appendages derive from set aside clusters of cells called imaginal discs and histoblasts that are located within the larval body but do not contribute to the larval morphology (Madhavan and Schneiderman 1977). In other species, cellular turnover is less drastic although the morphological change can be equally spectacular (Svácha 1992; Tanaka and Truman 2005). Because metamorphosis is a time of cellular reprogramming and major morphological changes, it has been molded by natural selection in unique ways to accommodate distinct life history strategies.

In many metamorphic species, the environment encountered during their juvenile development often alters the adult phenotype. In these species, cues from the environment are often used to fine-tune the metamorphic transformation. By flexibly modifying the final adult morphology, organisms can ensure that their adult morphology and behavior are maximally adapted to the particular environment they occupy. This ability to adjust the developmental trajectories in organisms with complex life cycles is called developmental plasticity. Developmental plasticity plays a particularly important role in terrestrial animals where abiotic conditions can change dramatically from one season to the next. Recent studies in insects have begun to identify the mechanisms underlying developmental plasticity. In this chapter, we discuss the adaptive significance of developmental plasticity in different species of insects and the mechanisms underlying this process.

3.1.2 *Metamorphosis Is the Time for Reprogramming*

Although in amphibians and many marine invertebrates, metamorphosis is an ancestral developmental strategy, in insects, metamorphosis is a derived trait that evolved after land colonization (Bradley et al. 2009). The life history of the earliest insects was most likely similar to that of current wingless orders, such as Zygentoma (silverfish) (Grimaldi and Engel 2005). Typically, these insects are classified as ametabolous insects. Ametabolous insects undergo direct development where their external morphology remains essentially unchanged throughout their development (Fig. 3.1a) (Erezyilmaz 2006). The first major morphological innovation that paved the way for insect diversification and radiation was the evolution of flight ability, which eventually facilitated the evolution of incomplete metamorphosis or hemimetaboly (Kukalova-Peck 1978; Truman and Riddiford 2002; Belles 2019; Truman 2019). Phylogenetic and paleontological data indicate that the evolution of wings and hemimetaboly coincided during early Devonian and that the two events are likely linked (Carpenter 1992; Truman and Riddiford 1999; Misof et al. 2014). In hemimetabolous insects, the immature juvenile stages, nymphs, resemble the adult

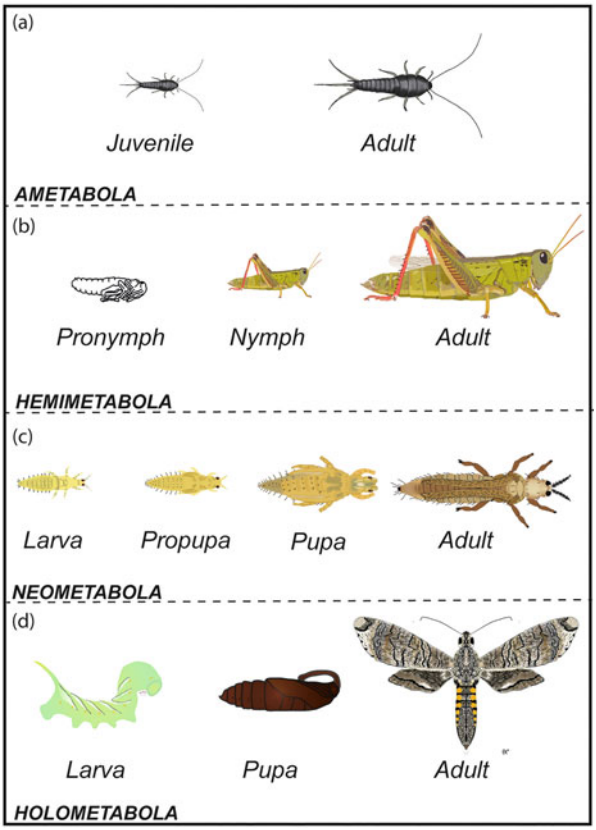

Fig. 3.1 Life history strategies in insects. (**a**–**d**) Different life history strategies, represented by silverfish (**a**), grasshoppers (**b**), thrips (**c**), and hornworms (**d**)

but lack functional wings and genitalia (Fig. 3.1b). The nymphs and adults usually share the same habitat and food resources, which can lead to potential competition between nymphal growth and adult reproduction. Some hemimetabolous insects evolved strategies to mitigate this competition. For example, aquatic nymphs and adults of dragonflies and mayflies explore very different ecological niches, and thrips and some hemipterans show a quiescent stage between the juvenile and adult stages so that the two do not coexist at the same time in the same niches (neometaboly, Fig. 3.1c). However, the complete separation of life stages into independent modules, with the capacity to evolve and adapt independently, only became possible in the early Carboniferous period when complete metamorphosis, or holometaboly, evolved (Truman and Riddiford 1999, 2019; Rainford et al. 2014). The holometabolous larvae never have external rudiments of wings or genitalia because they usually develop from internal groups of undifferentiated or partially differentiated cells called the imaginal cells or imaginal primordia (Sehnal et al. 1996; Truman and Riddiford 2002; Tanaka and Truman 2005). The radically different morphologies of larvae and adults are separated by a transitional, non-feeding and usually immotile stage called pupa (Fig. 3.1d).

The evolution of complete metamorphosis is thought to be a key innovation that facilitated the rapid adaptive radiation of insects (Yang 2001). The evolution of reprogramming of external and internal structures allowed larvae and adults to explore different niches and food resources. During metamorphosis, adult appendages, such as wings, legs, eyes, antennae, and genitalia, and internal organs, such as intestine and trachea, develop from imaginal cells and primordia. At the same time, larval tissues are eliminated by programmed cell death and autophagy during metamorphosis (Tanaka and Truman 2005). Because of this dynamic reprogramming at metamorphosis, holometabolan insects undergo dramatic morphological changes and develop into adults that are highly adapted for reproduction and migration. In addition, holometabolan adults typically do not further grow once emerged, presumably because the gland necessary for molting degenerates (Kamsoi and Belles 2020; Jeng et al. 2021). Thus, adult size is essentially determined at the end of the larval stage. Accordingly, metamorphosis is a reprogramming process that separates growth and reproduction in holometabolous insects.

3.1.3 How the Larval Environment Impacts Metamorphosis

The larval environment can impact metamorphosis in two broad ways. First, the larval environment can impact the timing of metamorphosis and alter the size of the adult organism and the phenology of life history traits, such as the timing of reproduction and diapause. Because adults do not grow in size, larval growth and metamorphic timing are directly related to the adult size: if larvae are induced to undergo metamorphosis earlier, the adults will be substantially smaller than if they had a longer feeding period. Given that size has important impacts on both survival

and reproduction of adults, larval environments can have important fitness consequences (Honěk 1993; Blanckenhorn 2000).

Alternatively, the larval environment can also influence developmental plasticity at metamorphosis, leading to two or more distinct adult morphologies. When these phenotypes are adapted to the particular environment that the adult insect encounters, the plastic developmental response is called a polyphenism (Moran 1992). Polyphenisms are regulated by a switch-like mechanism that generates discontinuous phenotypic responses to environmental changes (Nijhout 1999, 2003a). The sensitive period for insects occurs during the larval stage when a variety of environmental cues are sensed by the growing insect. The larval stage often lasts a long time and is well suited to collect information about the environmental condition. The cumulative environmental information is integrated by the neuroendocrine system, which alters development during metamorphosis.

A summary of the two ways by which the larval environment influences adult morphologies is shown in Fig. 3.2. In both cases, the larval environment is sensed in a cumulative manner. These inputs are then integrated by neuroendocrine centers that produce signals that travel to target tissues at the onset of, or during, metamorphosis to initiate the reprogramming of tissues. In cases where the larval environment impacts the timing of metamorphosis, the final adult size is altered (Fig. 3.2a). In polyphenisms, the reprogramming leads to distinct morphologies (Fig. 3.2b). These are not mutually exclusive, however, as larval environment impacts both the timing of metamorphosis and adult morphogenesis in most species.

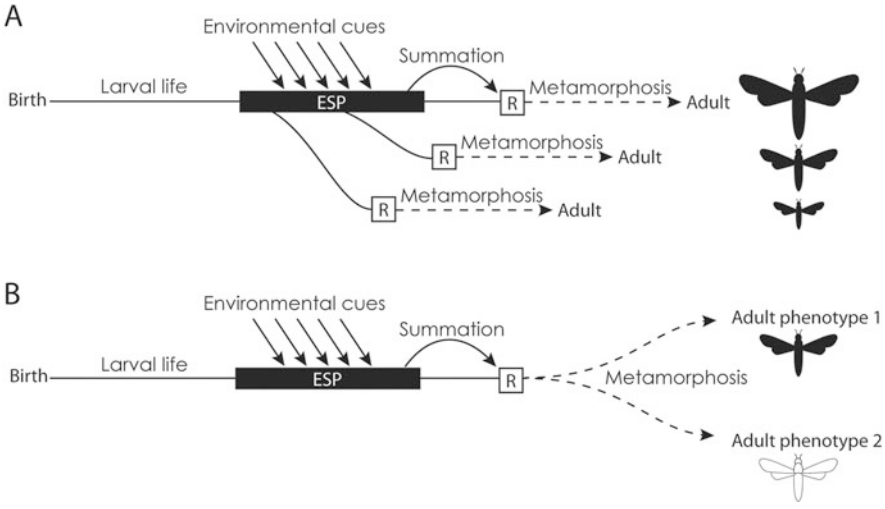

Fig. 3.2 Impacts of the larval environment on adult morphologies. Environmental changes encountered during the larval stage can impact adult morphology by shifting the timing of metamorphosis (a) or by altering the developmental trajectory during metamorphosis, an adaptive strategy called polyphenism (adapted from Nijhout 1999) (b). ESP = Environmental sensitive period; R = reprogramming

3.2 Whole Body Growth and Timing of Metamorphosis

3.2.1 Adaptive Significance of Body Size and Metamorphic Timing

A key consequence of altering the timing of metamorphosis is a change in adult body size. Adult body size has major impacts on survival and fitness of an organism. Within a given species, larger females tend to have higher fecundity (Honěk 1993; van Uitregt et al. 2012). The number of ovarioles scales positively with body size and in many cases, ovariole number is determined by resources available to the growing larva (Honěk 1993). In fact, ovariole number is partially influenced by the nutrition-sensitive insulin signaling pathway (Green and Extavour 2012). In addition, larger body sizes protect adults from desiccation and accumulate more resources that enhance survival and performance (Lighton et al. 1994). In males, larger body size tends to lead to higher reproductive fitness by shortening the copulation duration or increasing winning probability in male–male competition (Parker and Simmons 1994). There are also many forces that prevent organisms from becoming too large (Blanckenhorn 2000; Berger et al. 2006). For example, longer larval stage needed for a larger adult body size can increase predation, parasitization, and starvation risks. Energetic costs are higher for larger species as well (Blanckenhorn et al. 1995; Blanckenhorn 2000).

Within a particular species, life history strategies must adapt to the local seasonality. In many species, developmental time is maximized to ensure full use of the growth period available to a given population. In univoltine species, this leads to what is known as the "converse of Bergmann's rule" in which body size decreases with increasing latitude (Park 1949; Masaki 1967; Mousseau and Roff 1989). Species with many generations in one year follow Bergmann's rule, or more precisely James' rule, in which organisms attain larger body sizes at higher latitudes (James 1970; Blanckenhorn and Demont 2004). In species with a mix of univoltine and multivoltine populations, a sawtooth like pattern emerges (Roff 1980; Mousseau and Roff 1989). In addition to latitudinal differences, adaptations of body size and developmental time are also observed along an altitudinal gradient (Berner et al. 2004; Berner and Blanckenhorn 2006). For example, along an altitudinal gradient, higher elevation may constrain the growth period, leading to a more rapid growth rate and a smaller body size. Thus, the timing of metamorphosis and body size is shaped by selection imposed by both the environment and life history strategies. The mechanisms underlying such intraspecific variations are not yet well understood. However, species-specific mechanisms of body size determination have been well documented and species-specific adaptations to feeding ecologies have also been elucidated. The remainder of this section discusses these findings.

3.2.2 *Mediators of Metamorphic Timing and Growth*

3.2.2.1 Prothoracicotropic Hormone

Although many aspects of insect metamorphosis are still to be uncovered, precisely regulated endocrine signals that are sensitive to intrinsic and extrinsic stimuli play salient roles in the regulation of metamorphosis (Fig. 3.3) (Nijhout 1998). The fundamental knowledge of the endocrine control of metamorphosis was established by Sir Vincent B. Wigglesworth in the 1930s (Wigglesworth 1934b, 1954). Wigglesworth demonstrated the presence of humoral factors that control metamorphosis in the kissing bug *Rhodnius prolixus* using the classical heterochronic parabiosis, a technique used to physically connect living animals of different ages (Wigglesworth 1934b). The structures and basic functions of each of these factors were subsequently identified as prothoracicotropic hormone (PTTH, originally called brain hormone) (Wigglesworth 1934b), 20-hydroxyecdysone (20E, originally called molting hormone) (Fukuda 1941; Williams 1947), and juvenile hormone (JH,

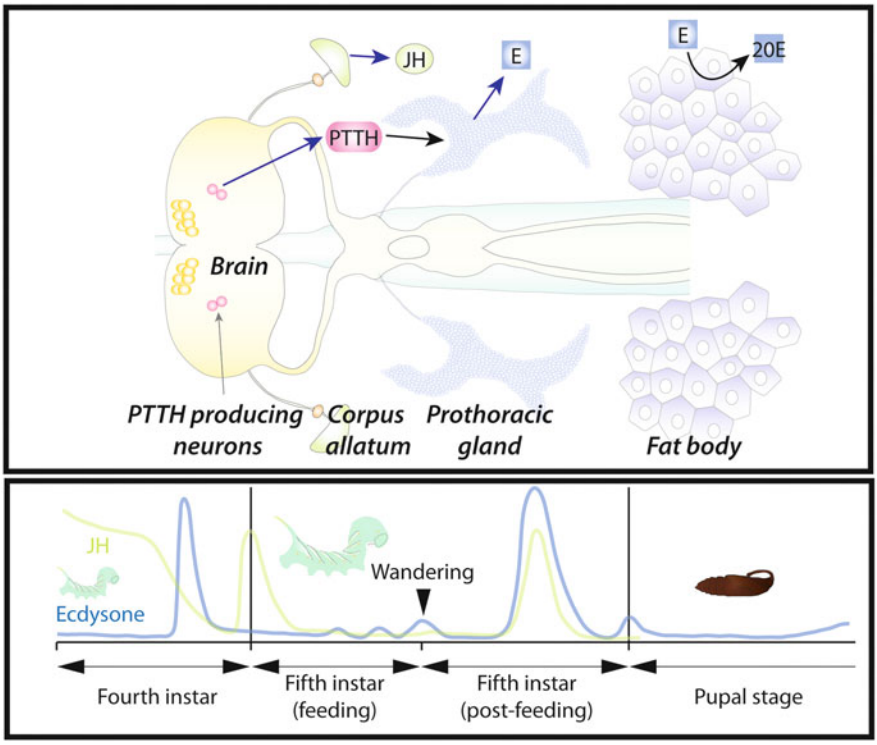

Fig. 3.3 Insect endocrine system. Top panel, brief scheme of endocrine organs that are involved in developmental hormone biosynthesis during larval stages, for lepidopterans (adapted from Nunes et al. 2020). Bottom, fluctuation of ecdysone and JH throughout *Manduca sexta* development (after Riddiford et al. 2003)

originally called “inhibitory hormone” and later considered as “*status quo* hormone”) (Wigglesworth 1934b).

The first experiments that demonstrated the involvement of the insect brain in the regulation of metamorphosis were conducted by Stephan Kopeć, using the gipsy moth *Lymantria dispar* (Kopeć 1922). Using classical ligation experiments that separate the developing body into anterior and posterior parts, Kopeć demonstrated that the anterior part (where the brain is located) was needed for a larva to molt into a pupa (Kopeć 1922). Later studies by Wigglesworth reached similar conclusions by showing that parabiosis of non-molting (decapitated, brainless) and molting (un-decapitated) juveniles of *R. prolixus* leads to signs of simultaneous molting (Wigglesworth 1934b). Implantation of various compartments of the brain into juveniles led Wigglesworth to determine the source of this brain hormone as the anterocentral portion of the brain.

It took 70 years after the work of Kopeć for the brain hormone, later designated as PTTH (Truman 1972), to be identified through classical biochemistry approaches using millions of heads of the silkworm, *Bombyx mori* (Kataoka et al. 1991). Since then, many studies have focused on the understanding of the mechanisms triggering PTTH secretion and mode of action. Pioneer work by Wigglesworth demonstrated that the distention of the intestinal tract in *R. prolixus* was the most important factor determining the timing of PTTH release in this species (Wigglesworth 1933). Although multiple smaller blood meals are insufficient to induce molting, artificially increasing distention by blocking the anus with paraffin is sufficient to decrease the volume of the blood meal required to trigger PTTH secretion (Wigglesworth 1933). Later, this process was shown to be controlled by abdominal stretch receptors not only in *R. prolixus* (Wigglesworth 1933) but also in insects that have a continuous rather than an episodic feeding habit, such as the milkweed bug *Oncopeltus fasciatus* (Nijhout 1979). However, in other insects, the conditions that influence PTTH secretion are still not completely understood. Furthermore, PTTH secretion also seems to be a gated phenomenon, as it occurs only during a specific time of the day and when critical criteria are met, such as size or weight (Nijhout and Williams 1974a; Nijhout 1981). The fact that PTTH secretion is gated suggests that molting and metamorphosis are influenced by the circadian clock (Truman and Riddiford 1974).

Once the conditions that trigger PTTH secretion are met, this hormone is released from specific neurosecretory cells in the brain (Fig. 3.3, top panels) (Steel and Vafopoulou 2006) and binds to its receptor Torso, which is specifically expressed in the prothoracic gland at the larval stage (Rewitz et al. 2009). After binding to its receptor, PTTH stimulates the secretion of the molting hormone, ecdysone, from the prothoracic gland.

3.2.2.2 Ecdysteroids

The endocrine pathway regulating molting was elucidated by the work of Carroll Milton Williams using the silkworm, *Hyalophora cecropia*. His work demonstrated

that in ligated animals, the posterior part could molt when the brain and prothoracic glands were co-transplanted, which led him to suggest that two endocrine factors from these two organs were required for molting (Williams 1948). This molting factor from the prothoracic gland was first purified by Butenandt and Karlson from *B. mori* pupae (Butenandt and Karlson 1954). They purified two very similar molting hormones, α-ecdysone and β-ecdysone.

α-ecdysone, now known as ecdysone, is a biologically less active hormone produced in the prothoracic gland. Once secreted, it is converted by peripheral tissues into the more biologically active form, β-ecdysone or 20-hydroxyecdysone (20E) (Fig. 3.3) (Gilbert and Goodman 1981). The prothoracic gland secretes ecdysone prior to each molt in response to PTTH stimulation. After secretion and conversion, 20E binds to the functional ecdysone receptor heterodimeric complex, Ecdysone Receptor (EcR) and Ultraspiracle (Usp), the homologue of the mammalian Retinoid X Receptor (Thummel 2001). This complex activates the transcription of a series of ecdysone response genes (Nijhout 1998; Thummel 2001).

Until the penultimate larval/nymphal instar, the ecdysteroid titer has a relatively simple profile, with a single large peak that triggers the molt to the next juvenile instar (Granger and Bollenbacher 1981; Gilbert et al. 1996; Nijhout 1998). However, in several holometabolan species, the pupal molt is generally preceded by a few peaks of ecdysteroids (Fig. 3.3, bottom panel), as is the molt from nymph to adult in hemimetabolans (Granger and Bollenbacher 1981; Gilbert et al. 1996; Nijhout 1998). Specifically, at least two pulses of ecdysteroids precede pupation. The first small peak, usually designated by "commitment," "wandering," or "reprogramming" peak, induces a series of changes that switch the developmental fate of the epidermis from a larval to a pupal program (Truman et al. 1974; Riddiford 1978, 2015). This ensures that the following peak will trigger the formation of the pupa or the adult, depending on the group of insects (Gilbert et al. 1996; Nijhout 1998). In addition to triggering commitment in epidermal cells, this ecdysteroid peak also triggers a set of behavioral alterations, particularly in holometabolans, the most dramatic of which are the engagement in wandering behavior, the cessation of the feeding period and the induction of a gut purge. The second, much larger peak, induces apolysis and the metamorphic molt (Fig. 3.3, bottom panels). Overall, the switch from juvenile to pupal or adult programs during the last juvenile molt requires the secretion and action of ecdysteroids. However, another necessary condition must be met: the absence of JH, as will be discussed next.

3.2.2.3 Juvenile Hormone

Using *R. prolixus,* Wigglesworth showed that decapitated third and fourth instar nymphs undergo precocious metamorphosis instead of waiting until the fifth instar to metamorphose (Wigglesworth 1934b). In contrast, transplantation of fourth instar corpora allata (CA) into final fifth instar nymphs triggered supernumerary juvenile molts, leading to the development of a sixth instar nymph with undeveloped functional wings and genitalia. Based on this evidence, Wigglesworth suggested

the existence of an anti-metamorphic hormone produced by the CA, that he designated "juvenile hormone" (JH), due to its capacity to maintain juvenile features and inhibit adult development (Wigglesworth 1934a, 1936).

JH is a sesquiterpenoid hormone involved in several aspects of development and reproduction, including regulation of metamorphosis (Riddiford 2012), caste determination (Wheeler and Nijhout 1981), diapause (Yin and Chippendale 1974), and ovarian development (Bloch et al. 2000). For larval/nymphal stages, it is generally assumed that JH defines the nature of molts. High concentrations of JH cause larval–larval or nymphal–nymphal molts in Holometabola and Hemimetabola, respectively, whereas low concentrations of JH are required to trigger pupation in Holometabola and adult molts in Hemimetabola (Gilbert et al. 1996; Nijhout 1998). Although much is still unknown regarding the molecular mechanisms through which JH regulates metamorphosis (Riddiford 2008), in dipterans this hormone functions through the intracellular receptors Methoprene tolerant (Met) and Germ cell expressed (Gce) but only through Met in many hemi- and holometabolans (Konopova and Jindra 2007; Jindra et al. 2015). After binding to the receptors, JH activates the expression of the transcription factor *Krüppel homolog 1* (*Kr-h1*) (Minakuchi et al. 2008), which ultimately induces the expression of a set of JH-sensitive downstream genes (Minakuchi et al. 2008, 2009).

In hemimetabolous insects, JH levels drop at the end of the last nymphal instar to allow for the formation of the adult. JH is cleared from the hemolymph at the last larval stage in Holometabola, but it increases again during the prepupal (wandering) peak of ecdysteroids (Fig. 3.3, bottom panel) (Gilbert et al. 1996). This redeployment ensures that tissues undergo a pupal molt instead of an adult molt directly and that cell patterning for adult structures is not switched on by the high levels of 20E characteristic of this stage (Truman and Riddiford 2007; Urena et al. 2016).

JH is necessary to prevent precocious metamorphosis until insects attain species-specific size before metamorphosis (Nijhout 1998; Riddiford 2012; Jindra et al. 2013). Providing exogenous JH to final instar larvae often induces supernumerary molts. Consistently, surgical removal of the corpora allata (called allatectomy) from penultimate instar larvae often induces precocious metamorphosis and produces miniature adults in many holometabolous species (Fukuda 1944; Suzuki et al. 2013). However, depletion of JH by various techniques in a wide range of species fails to induce precocious metamorphosis in very young larvae (Fukuda 1944). For example, in *B. mori*, whereas allatectomy using penultimate fourth or third instar larvae induces precocious metamorphosis, the same procedure on second instar larvae fails to induce precocious metamorphosis (Fukuda 1944). Instead, second instar allatectomized larvae molt to the third instar, and then undergo metamorphosis (Fukuda 1944). Similarly, neck-ligation, which separates the source organ of JH corpora allata from the rest of the body, induces precocious pupation during the third instar but not during the second instar (Bounhiol 1938). Furthermore, null mutant larvae of JH biosynthesis genes or JH signaling components, such as JH receptor *Met*, do not induce any signs of pupal characteristics during the first and second instars (Tan et al. 2005; Daimon et al. 2015). These studies show that although JH is necessary to maintain larval features after several larval molts, these characteristics

seem to be maintained independently of JH during early nymphal/larval instars (Smykal et al. 2014; Daimon et al. 2015).

In contrast, larval tissues of very young instar larvae seem to have the ability to show pupal characteristics. Classic transplantation experiments suggest that when the epidermis of first instar larvae of the wax moth *Galleria mellonella* is transplanted into the last instar larvae, the integument produces pupal cuticles at the time the host metamorphoses (Piepho 1938a, b) suggesting that as long as the host larva's humoral condition is appropriate, the implants have the ability to be pupally committed and to undergo metamorphosis. Moreover, very young larvae seem to either lack a humoral factor necessary to become pupae or have a secondary humoral factor that inhibits larval-pupal metamorphosis. A recent study using *B. mori* showed that the epidermis of neonate larvae produces pupal and adult cuticles when transplanted host animals undergo larval-pupal and pupal-adult molts, respectively. In addition, the authors showed that implantation of the epidermis of JH receptor Met mutant larvae into the penultimate instar wild type larvae that retain high JH concentrations, the epidermis can produce pupal cuticle (Inui and Daimon 2017). Thus, the authors proposed that the epidermis from very young larvae can show pupal characteristics when it is exposed to the hemolymph containing a humoral factor(s) that appears only in late larval stages. Importantly, JH seems to block the action of this humoral factor(s) to postpone the timing of metamorphosis until developing larvae reach a certain size. This unidentified factor is now known as competence factor, which, alongside with ecdysone, JH and PTTH, seems to play an essential role in the determination of the timing of metamorphosis in some insects.

3.2.2.4 Insulin/Insulin-Like Signaling/TOR Signaling Pathways

Body size is a complex trait that is modulated by many genetic and environmental factors. Rearing insects on low quality food or restricted amounts of nutrients leads to the production of drastically smaller body sizes (Davidowitz et al. 2004; Nash and Chapman 2014). In insects, as well as in other taxa including mammals, the key mediator of nutritional inputs is the Insulin/Insulin-like signaling (IIS) and target of rapamycin (TOR) signaling pathways (Britton et al. 2002; Ikeya et al. 2002; Wullschleger et al. 2006).

The IIS pathway regulates growth rate in most, if not all insects. Much of our understanding of IIS comes from work done on *Drosophila melanogaster* (Koyama et al. 2020). Eight *Drosophila* Insulin and Insulin-like peptides (DILPs) have been identified, and the number of ILPs can be quite large depending on the species (Nässel and Broeck 2016). Only one of the eight DILPs, DILP7, appears to have homologues in other species. Although ILPs can be secreted from various tissues (Brogiolo et al. 2001), the primary production site appears to be the neurosecretory cells in the brain, the insulin-producing cells (IPCs), which are also the source of ILPs in other species (Nässel and Broeck 2016; Koyama et al. 2020). Although DILPs produced by other tissues also play a critical role in regulating body size by

mediating inter-organ communication (see next section), we focus on the main nutrient-dependent regulation of the IIS pathway in this section.

Briefly, IIS pathway is activated by the intake of sugars or amino acids, which leads to the production of ILPs (Park et al. 2014). In adults, this link appears to be direct: adult IPCs are able to sense glucose in a cell autonomous manner (Kreneisz et al. 2010). In contrast, in larvae, nutrient sensing appears to be indirect with amino acids being sensed in the fat bodies and sugars being sensed in the corpora cardiaca (see next section for more details) (Colombani et al. 2003; Geminard et al. 2009; Kim and Neufeld 2015). These remote sensors then secrete factors that relay the nutrient-dependent signals to the IPCs (Nässel and Broeck 2016). The IPCs secrete DILPs, which travel to target tissues where they bind to the Insulin receptor (InR), a receptor tyrosine kinase that activates a signal transduction cascade (reviewed in Koyama et al. 2020). Activated InR phosphorylates the homolog of the mammalian Insulin Receptor substrate (IRS), Chico. Chico then activates phosphatidylinositide3-kinase (PI3K), which converts phosphatidylinositol (4,5)-biphosphate (PIP2) into the second messenger phosphatidylinositol (1,4,5)-triphosphate (PIP3). Phosphatase and tensin phosphatase (PTEN) catalyzes the reverse reaction. PIP3 activates protein kinase B/Akt, which phosphorylates the forkhead transcription factor Forkhead box O (FoxO). Phosphorylated FoxO leaves the nucleus and moves to the cytoplasm (reviewed in Koyama et al. 2020).

Another critical regulator of nutrient-dependent cell signaling is the TOR pathway, which is primarily sensitive to amino acids (Wullschleger et al. 2006). The TOR pathway begins with the activation of the small GTPase RHEB (Ras homologue enriched in the brain) in response to amino acids. RHEB then activates TOR kinase (Saucedo et al. 2003; Zhang et al. 2003). TOR kinase phosphorylates the ribosomal protein S6 kinase (S6K) and 4E-Binding Protein (4EBP), a translational repressor, which becomes inactivated when phosphorylated (Miron et al. 2003). The TOR signaling pathway appears to interact with IIS pathway in a complex manner and likely regulated in a tissue- and stage-specific manner (Oldham and Hafen 2003; Dong and Pan 2004; Wullschleger et al. 2006).

Mutating components of the IIS/TOR pathways alters the larval growth rate and ultimately alters the final adult body size by changing the cell size and the total cell count. Ablation of IPCs leads to growth retardation of larvae (Rulifson et al. 2002). These cells produce DILP2, whose overexpression can cause overgrowth of the body (Brogiolo et al. 2001). When InR or Chico is mutated, the resulting adult is reduced in size and has smaller and fewer cells (Bohni et al. 1999; Brogiolo et al. 2001), whereas PTEN mutant larvae develop into larger flies (Oldham et al. 2002). At the whole organism level, IIS regulates the growth rate and its impairment leads to a reduced growth rate and a longer growth period (Shingleton et al. 2005). Downregulation of TOR signaling in the fat body also leads to reduced growth rates (Colombani et al. 2003). Downregulation of IIS/TOR signaling pathways has been shown to slow growth rates in other insects (Hatem et al. 2015; Al Baki et al. 2018; Scieuzo et al. 2018).

Although growth rate can alter the final body size, the timing of growth cessation is another key variable that impacts the final adult body size. Ecdysteroids terminate

the growth phase by initiating the metamorphic transition, the cessation of feeding and the clearing of the gut (Truman 1972; Nijhout 1976). When the production of ecdysteroids, or response to ecdysteroids, is altered, the timing of metamorphosis is affected, either by truncating or delaying metamorphic entry. By changing the timing of metamorphosis, the feeding period is altered, consequently also impacting the final larval body size. As ecdysteroids are involved in metamorphic transition of virtually all holometabolous insects, ecdysteroids likely also regulate the termination of the growth period. Together, insulin and ecdysteroid signaling account for the growth rate and the final termination of growth period. As will be discussed below, these two signaling pathways appear to interact, but the extent to which these pathways influence each other largely depends on the species studied and the extent to which JH modulates the production and release of the other two hormones.

3.2.2.5 Interorgan Communication that Coordinates Growth

Animals sense changes in both external and internal conditions and adjust their developmental program accordingly. If the environment is unfavorable (for example, if food or oxygen supply is scarce), developing larvae often grow slower. However, this decrease in growth rate is accompanied by an extension in the duration of feeding period to ensure that impact on their final body size is minimized. These external and internal fluctuations are often sensed by specific organs/cells, which in turn signal to the whole body to adjust developmental programs via endocrine pathways. This inter-organ communication allows organisms to adapt to changes in extrinsic and intrinsic conditions by orchestrating development and physiology of the rest of the body.

One of the central organs sensing nutritional conditions in developing insects is the fat body, an insect's organ functionally homologous to mammalian adipose and hepatic tissues. The fat body is also the primary energy and nutrition storage tissue. It also acts as a central endocrine organ, releasing a number of endocrine factors into circulation in response to the intracellular nutritional condition in *D. melanogaster* (Colombani et al. 2003). When intracellular nutrition level is sufficient, the fat body releases endocrine signals so-called fat body-derived factors to regulate DILP secretion from the IPCs in the brain (Britton and Edgar 1998; Colombani et al. 2003; Geminard et al. 2009). In response to intracellular amino acid concentrations via the TOR pathway, this tissue releases a number of signaling molecules, such as Growth-blocking peptide (GBP) 1 and GBP2 (Koyama and Mirth 2016), Stunted (Sun) (Delanoue et al. 2016), and the TNF-alpha homolog Eiger (Agrawal et al. 2016) (Fig. 3.4). These factors have the capacity to control transcription and secretion of DILPs, acting both directly and indirectly on the IPCs. Sun and Eiger act directly on the IPCs by binding to the receptors Methuselah and Grindelwald, respectively (Agrawal et al. 2016; Delanoue et al. 2016). In contrast, GBP1 and GBP2 can act either directly via the receptor Mthl10 on the IPCs (Sung et al. 2017) or activate EGF-receptor in neurons that directly contact with these neurosecretory cells (Meschi et al. 2019).

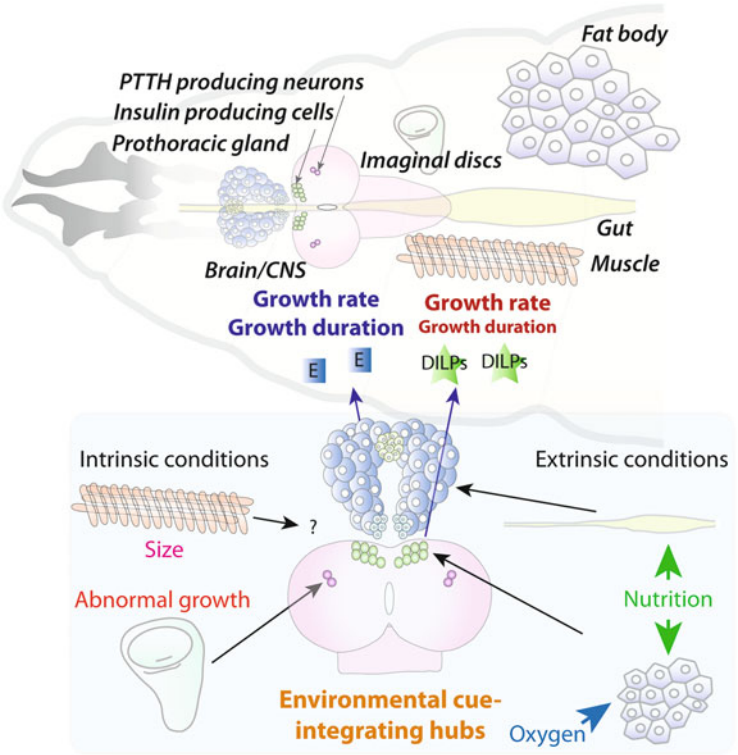

Fig. 3.4 Integration of environmental and internal cues for growth regulation via inter-organ communication in *Drosophila* larvae. Top panel, diagram of larval organs necessary for growth regulation. Bottom panel, inter-organ communications that regulate insulin, PTTH, and ecdysone production

Sugar and/or lipid concentrations are also sensed in the fat body, resulting in the production of other factors that have the capacity to remotely regulate DILP translation and secretion (Fig. 3.4). The neuropeptide CCHamide-2 (CCHa2) is a TOR-dependent peptide that is primarily sensitive to internal sugar concentrations (Sano et al. 2015). CCHa2 acts directly on the IPCs via its receptor CCHa2-R, stimulating DILP secretion and growth. The leptin-like factor Unpaired-2 (Upd2) also regulates DILP secretion in response to dietary sugar and lipids (Rajan and Perrimon 2012). Upd2 indirectly regulates DILP secretion by binding to the receptor, Domeless, expressed in GABAergic neurons adjacent to the IPCs. This binding results in the relief of the inhibitory activity of these neurons, ultimately positively regulating the secretion of DILPs.

Besides these fat body-derived factors that control DILP transcription and secretion in the IPCs, the fat body also produces factors that modulate insulin signaling activity in the whole body. For example, both acid-labile subunit (ALS) and imaginal morphogenesis protein-late 2 (ImpL2) bind DILPs in the circulating

hemolymph, antagonizing their activity as a mechanism to fine-tune insulin signaling systemically (Arquier et al. 2008; Honegger et al. 2008; Droujinine and Perrimon 2016; Nässel and Broeck 2016). The fat body also produces one of the DILPs, DILP6, upon the cessation of feeding to promote growth, both in prepupal and pupal stages and under starvation conditions in larvae and adults (Okamoto et al. 2009; Slaidina et al. 2009). DILP6 acts as a molecular switch between the promotion of energy storage and growth (Okamoto et al. 2009; Slaidina et al. 2009), regulating both directly and indirectly the secretion of brain-derived DILPs (Bai et al. 2012).

The fat body also senses another crucial environmental factor for growth, oxygen concentration (Fig. 3.4). Similar to nutrition, hypoxia causes reduced growth rate and delayed metamorphosis in *D. melanogaster*. The fat body senses internal oxygen concentrations and controls DILP secretion from the IPCs through an unidentified humoral factor(s) (Texada et al. 2019). In contrast to TOR-dependent regulation of the majority of nutrition-dependent fat body-derived factors, hypoxia controls DILP secretion through a factor(s), whose expression is dependent on the hypoxia-inducible factor 1α (HIF-1α). This HIF-1α-dependent regulation is likely even more effective than regulation of nutrition- and TOR-dependent DILP secretion (Texada et al. 2019). In *Manduca sexta*, oxygen concentration is thought to act as a cue for achieving a specific size known as the critical weight (see below) (Callier and Nijhout 2011). It is not clear whether the fat body mediates this critical weight achievement in this species.

In addition to the fat body, the intestine also senses nutritional conditions in insects. *D. melanogaster* larval enterocytes in the gut respond to dietary nutrients and produce Hedgehog (Hh) to regulate ecdysone production in the prothoracic gland as well as to act on the fat body to reduce growth rate (Rodenfels et al. 2014) (Fig. 3.4). Nutritional information is also sensed in the enteroendocrine cells of the gut in insects. In *D. melanogaster*, these cells produce one of the ligands of transforming growth factor-β (TGF-β), Activin, in high concentrations of dietary sugar during the larval stage (Song et al. 2017). Once secreted, Activin acts on the fat body and affects adipokinetic hormone (AKH) signaling, which mobilizes stored nutrition in this tissue. However, it is not clear whether this mobilization of nutrients in larval stages affects adult life history.

In addition to the fat body and intestine, at least in *M. sexta* and *Tribolium castaneum*, developing musculature is used as a proxy of larval size to regulate the timing to be the last larval instar. In *M. sexta*, mass of the musculature becomes above certain threshold that correlates with the attainment of threshold size, the developmental checkpoint that occurs in the penultimate larval instar (He et al. 2020). Once larvae attain this developmental checkpoint, they molt to the final larval instar after the following larval–larval molt (He et al. 2020). This larval musculature mass correlates with the amount of the TGF-β ligand, Myoglianin (Fig. 3.4). In *T. castaneum*, knockdown of *myoglianin* by RNAi results in failure to undergo metamorphosis and *myoglianin* knocked down larvae repeat supernumerary molts permanently. This occurs presumably due to disrupted signaling communication between the muscle and rest of the body necessary for threshold size attainment

(He et al. 2020). Therefore, the amount of muscle tissues appears to affect the final body size, similarly to the fat body-derived factors.

3.2.3 *Effects of Nutrition on Body Size and Developmental Timing*

Because the pupa does not feed and the adult typically does not molt, the size at which the larva stops feeding and enters metamorphosis dictates the adult size. Larval growth is regulated by three parameters: the growth rate, decision to undergo metamorphosis, and interval between this decision point and the secretion of ecdysone, which ceases growth (Nijhout et al. 2006). Growth rate is an important component of larval growth and has important consequences on the final larval size. Nutritional intake can drastically alter the growth rate although additional factors, such as temperature, humidity and presence of predators, can also have large impacts on growth rates (Davidowitz et al. 2003; van Uitregt et al. 2012).

The timing of metamorphic entry is determined by a series of developmental events. Although the mechanism of metamorphic entry varies drastically between species, in many cases it involves some sort of size sensing events during which the larval size is assessed. In the tobacco hornworm, *M. sexta*, which has served as a major model for body size determination, three distinct size assessment checkpoints have been identified: the threshold size (or threshold weight), the minimum viable weight, and the critical weight. The threshold size is the size at which the larva decides to enter the final larval instar (Nijhout 1975). If the larva has not attained the threshold size, it will undergo an extra larval molt(s) before entering the final instar. The minimum viable weight is the size at which starvation still permits the larva to survive to metamorphosis; starvation below this weight leads to death (Mirth et al. 2005; Mirth and Riddiford 2007; Callier and Nijhout 2013; Xu et al. 2020). The critical weight is the weight above which starvation no longer delays metamorphosis (Nijhout and Williams 1974b). When larvae are starved above the minimum viable weight and below the critical weight, the onset of metamorphosis is delayed. Note that the minimum viable weight and critical weight are experimentally defined—that is, they are identified by starving the larvae. The critical weight is not a fixed measure, but rather a function of the weight and size of the animal at the time of the previous molt. The threshold size, in contrast, can be detected without starving larvae (He et al. 2020).

The cessation of growth is typically marked by entry into the prepupal phase. At this point in development, the larva typically clears its gut in preparation for remodeling the gut. From this point onward, the larva no longer feeds, and the final size of the adult is set. The period between the time of critical weight attainment and cessation of feeding is called the terminal growth period, which marks the final phase of larval growth (Davidowitz and Helm 2014).

While growth rate can certainly influence the final adult body size, metamorphic timing is regulated in principle by the three size checkpoints. Therefore, we focus mostly on how larval feeding environments impact the checkpoints and the timing of metamorphosis. *M. sexta* has served as an important model for identifying major checkpoints involved in growth regulation. It turns out, however, that the mechanisms involved in growth regulation—in particular the decision to stop growing—are diverse and adapted to feeding ecology of different species. Here, we will attempt to synthesize the current knowledge into three different categories to make sense of the diversity of size regulators. These adaptive strategies mitigate trade-offs between reproductive output and survival and appear to have evolved in response to specific feeding ecologies of particular insects.

3.2.3.1 Body Size Check Determination in Insects with Abundant Food Source

The first strategy involves maximizing growth at the expense of developmental speed. Such species tend to have abundant food sources and will feed until they attain a particular size threshold. Starvation below this threshold delays development and triggers the larva to search for food. Because food sources are abundant, the larvae will eventually find food and resume growth until the size threshold is reached.

Such a strategy is observed in *M. sexta*. Threshold size in this species appears to be attained at the end of the fourth instar (Nijhout 1975; He et al. 2020). If the larva has not attained the threshold size, it will delay entry into the final instar by inserting an extra larval instar (Kingsolver 2007). This has considerable impact on the final size as the addition of a larval instar adds additional time to feed and grow. The threshold size in this species can shift through artificial selection for larger or small body sizes (Grunert et al. 2015) and appears to be correlated with the attainment of a particular muscle size (He et al. 2020).

Once the larvae have attained the threshold size and molt into the final instar, JH plays a prominent role in determining the timing of metamorphosis. High levels of JH present at the onset of the final instar have been shown to delay the attainment of the minimum viable weight (Xu et al. 2020). Once the larvae have fed enough, JH levels drop and ecdysteroid biosynthesis genes are activated at minimum viable weight (Xu et al. 2020). This basal ecdysteroid biosynthesis is sufficient to promote eventual metamorphic entry under starvation conditions; however, starvation delays the timing of metamorphic onset because starvation decreases ecdysteroid biosynthesis rate by inhibiting ecdysone biosynthesis gene expression (Nijhout 1976; Callier and Nijhout 2011, 2013; Xu et al. 2020). In normally feeding larvae, the timing of critical weight attainment appears to be correlated with the onset of clearing of JH from the hemolymph (Nijhout and Williams 1974a; Suzuki et al. 2013). Because JH is not cleared until critical weight has been attained, the presence of low amounts of JH prevents the onset of metamorphosis by inhibiting PTTH production from the brain (Nijhout and Williams 1974a; Browder et al. 2001; Suzuki

et al. 2013). Thus, in this species, starvation delays the onset of metamorphosis and ensures that the larva becomes as large as possible before metamorphosis.

3.2.3.2 Body Size Check Determination in Insects with Ephemeral Food Source

The second strategy involves maximizing developmental speed at the expense of body size. Species with this strategy tend to have rapid life cycles with the goal of reproducing as quickly as possible. Such life history strategies are seen among species that have ephemeral food sources and cannot afford to delay metamorphosis when food runs out. *D. melanogaster*, whose rapid life cycle has led to their prominence as a genetic model system, uses this strategy to develop as quickly as possible. In this species, the life cycle is already rapid under normal feeding conditions, but development speeds up even more when food is removed so that they can successfully survive to pupation (Beadle et al. 1938; Stieper et al. 2008; Koyama et al. 2014). Interestingly, selection for a rapid life cycle appears to have led to the convergence of the minimum viable weight and the critical weight, thus at no time in their development can larvae be starved to delay metamorphosis without killing them (Mirth et al. 2005). In this species, therefore, size is no longer a key factor in the decision to undergo metamorphosis. Instead, once larvae have eaten enough to survive metamorphosis, larval development progresses in a clock-like fashion, ensuring that larvae enter metamorphosis without any delays (Ohhara et al. 2017).

In this species, metamorphic timing is regulated by a nutrient-sensitive process that modulates ecdysteroid production. Ecdysteroid biosynthesis genes are activated at the minimum viable weight/critical weight checkpoint (Koyama et al. 2014; Ohhara et al. 2017). Several studies indicate that altering IIS/TOR signaling in the prothoracic glands could alter the production of ecdysteroids and hence the minimum viable weight/critical weight checkpoint (Caldwell et al. 2005; Mirth et al. 2005; Layalle et al. 2008; Koyama et al. 2014; Ohhara et al. 2017). When IIS/TOR signaling is inhibited in the prothoracic glands, ecdysteroid biosynthesis is delayed and the minimum viable weight/critical weight checkpoint shifts to a larger size. Once ecdysteroidogenesis begins, TOR signaling becomes dispensable and starvation can no longer inhibit ecdysteroid biosynthesis, leading to the loss of developmental delays. Instead, a timer-like mechanism takes over, allowing the prothoracic glands to dictate the timing of metamorphosis regardless of the body size (Ohhara et al. 2017). JH levels are barely detectable during the early portion of the final instar and do not delay the timing of minimum viable weight as it does in *M. sexta* (Xu et al. 2020).

3.2.3.3 "Bail Out" Strategy

Finally, there are species that appear to use a combination of these two strategies. In such species, as long as food is available, they will continue to feed until a size threshold is reached. However, once starved, they initiate a clock-like mechanism to initiate metamorphosis as soon as possible. This mechanism is called the "bail-out" mechanism and can be seen as enjoying the benefits of both of the aforementioned strategies. This strategy ensures that the larvae grow as large as they can when food is abundant; but when their food runs out, they switch to developing as quickly as they can. Such life history strategies are observed among species with food that is provisioned by their parent. Dung beetles provide their offspring with dung balls, which can be variable in size. If the unlucky offspring ends up with a tiny dung ball, it has no option but to metamorphose once the food runs out. In such cases, the larvae will "bail-out" and initiate metamorphosis quickly (Shafiei et al. 2001). In contrast, a lucky larva provisioned with a large dung ball will continue to eat until it has reached a large body size. Similar bail-out type strategies have been documented in beetles, such as the longicorn beetle *Psacothea hilaris* (Nagamine et al. 2016), and hymenopterans, such as *Osmia lignaria* (Helm et al. 2017). In the flour beetle *T. castaneum*, prolonged feeding on low quality diet can also lead to the eventual metamorphosis of the larvae in sub-threshold size animals, potentially reflecting a bail-out type strategy in this species as well (Chafino et al. 2019).

The solitary bee *O. lignaria* has been used to probe the mechanism underlying this strategy (Helm et al. 2017). In this species, the mechanism underlying metamorphosis appears to involve a combination of the two mechanisms described above. JH appears to delay the onset of metamorphosis when food is abundant (Helm et al. 2017), presumably by delaying the attainment of the minimum viable weight. However, once food is removed, or if JH is depleted chemically, the larvae quickly initiate metamorphosis in a clock-like fashion. Regardless of the weight attained, larvae will always initiate metamorphosis within 24 h of removal of food (Helm et al. 2017). Thus, in this species, a timer-like mechanism is activated by starvation, presumably by shutting off JH. The timer is similar to that of *D. melanogaster* where ecdysteroid biosynthesis is activated and becomes nutrient-independent although studies on Halloween genes are needed to support this notion. Although starvation can induce the timer at any point in the final instar of *O. lignaria*, in other species, starvation cannot induce a timer until a certain size checkpoint, indicating that the timer is not necessarily triggered by starvation in all species that use a bail-out strategy (Nagamine et al. 2016).

3.2.3.4 JH Mediates Distinct Feeding Ecology of Insects

A summary of the strategies used is shown in Fig. 3.5a. Some species prioritize developmental speed over adult body size whereas others prioritize adult body size at the expense of developmental time. Others have evolved strategies to balance the

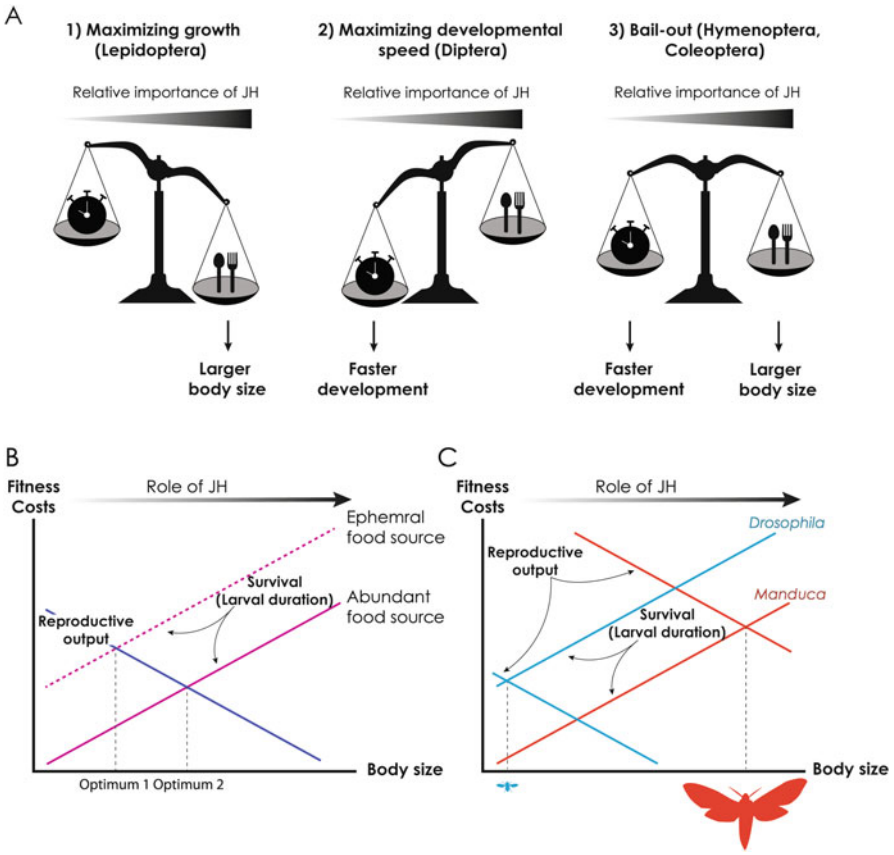

Fig. 3.5 Trade-offs between survival and reproductive outputs shape body size. (**a**) Three distinct strategies for mediating trade-offs between reproduction (favored by larger body size = denoted by the fork and knife) and survival (favored by faster development = denoted by the clock). Each of these strategies is adapted to the particular feeding ecology of the species. JH mediates the trade-offs and determines the degree to which attainment of a larger body size predominates over faster development. (**b**, **c**) A model depicting fitness costs arising from having different body sizes. The larger the body size, the higher reproductive output and therefore reduced fitness costs (represented by the dark blue reproductive output line). However, a higher body size comes at the cost of having to grow for a longer period of time (represented by the red survival/larval duration line). The optimum body size is where the fitness costs from reproduction and developmental time are minimized. (**b**) Populations encountering ephemeral food sources have higher survival/larval duration costs because longer developmental time risks death (dotted red line). These populations have lower optimal body size (Optimum 1). In populations with abundant food supply, the survival/larval duration line shifts to the right, accompanied by an increased role of JH during the larval stage (solid red line). Such populations have higher optimal body size (Optimum 2). (**c**) In addition to the shift in the survival/larval duration line, each species has its own reproductive output line. In the case of *D. melanogaster*, this line is shifted to the left such that the optimum body size is very small (light blue). In *M. sexta,* the two lines cross at a much higher body size, leading to the very large adult body size

two trade-offs. These distinct strategies arise through changes in the relative importance of a developmental timer and nutrient sensitivities in determining the metamorphic timing. The presence of JH appears to mediate the two processes by favoring a nutrient-sensitive mechanism that prioritizes body size over speed (Suzuki et al. 2013; Hatem et al. 2015; Nijhout 2015).

More generally, we propose that different species have evolved optimal strategies to maximize reproduction while reducing fitness costs of a longer life span (Fig. 3.5b,c). Graphically, this can be represented using a model similar to the supply and demand model of economics. In this model, the X-axis represents the body size of the adult and the Y-axis represents fitness costs. In this plot, the fitness costs incurred from limited resources in the body decrease as the adult body size increases (represented by the reproductive output line); however, the cost of lengthening the larval growth period increases with increasing adult body size (represented by the survival line). The size at which the two lines meet represents the optimal body size for a given species. Depending on the strategy favored, the survival line can shift (dotted line in Fig. 3.5b), thus increasing or decreasing the optimal body size. Depending on the species, reproductive output line will also shift, thus the optimal body size can differ vastly (Fig. 3.5c). We propose that the role of JH during the larval stage becomes more prominent toward the right side of the graph and that JH plays a critical role in mediating the life history trade-offs between developmental time and reproduction.

3.2.4 *Effects of Tissue Regeneration on Developmental Timing*

As seen in other animals, many insects have genetic programs that allow them to alter their physiology and development for regeneration to cope with injury or abnormal tissue growth (Suzuki et al. 2019). In response to injury, developmental processes need to be adjusted to permit sufficient time for regeneration. Insufficient coordination between developmental time and regeneration potentially causes organ malformation, compromising organ structure and function.

Classical studies on several cockroach species, including *Blattella germanic*a, show that leg amputation during the juvenile (nymphal) stages induces developmental delay during nymphal development (O'Farrell and Stock 1954; Stock and O'Farrell 1954; Kunkel 1977). Similar phenomenon is also observed in holometabolous insects. In the wax moth, *Galleria mellonella*, partial removal of the developing adult wing leads to developmental delay at larval stages (Madhavan and Schneiderman 1969; Malá et al. 1987). In the fruit fly *D. melanogaster*, injury in developing larval organs also extends the duration of larval development (Bourgin et al. 1956; Stieper et al. 2008; Hackney and Cherbas 2014; Gontijo and Garelli 2018). Interestingly in the Mediterranean flour moth *Ephestia kuehniella*, implantation of a small fragment of developing wings into host larvae induces developmental

delays (Rahn 1972), suggesting that injured developing organs secrete a factor that changes developmental timing.

In *D. melanogaster*, this injury- or abnormal growth-dependent developmental delay in metamorphosis is primarily mediated by the relaxin-like peptide DILP8, that is produced in abnormally growing discs (Colombani et al. 2012; Garelli et al. 2012). Injury- or abnormally growing disc-derived DILP8 induces a developmental delay through the G-protein coupled receptor Lgr3, expressed in a pair of bilateral *pars intercerebralis* (PIL) neurons. These Lgr3 positive neurons inhibit secretion of PTTH by synapsing upon the PTTH producing neurons (Colombani et al. 2015; Garelli et al. 2015; Vallejo et al. 2015; Jaszczak et al. 2016). This inhibition of PTTH secretion results in reduction of ecdysone production from the prothoracic gland through the PTTH receptor Torso, which in turn results in delays in the timing of metamorphosis. Thus, this developmental checkpoint couples sufficient tissue growth with developmental timing.

In addition, this signaling pathway coordinates the size of all paired discs. Elimination of DILP8 or Lgr3 enhances asymmetric growth in paired organs (Garelli et al. 2012, 2015; Colombani et al. 2015), suggesting that the primary function of DILP8-Lgr3 signaling is likely a coordination of symmetric growth (Garelli et al. 2012). This asymmetric growth in DILP8 or Lgr3 mutants is likely due to lack of communication between a normally developing organ and an organ with small deviations in growth (Gontijo and Garelli 2018). If DILP8-Lgr3 signaling is normal and one of the developing organs shows any developmental error, this organ is expected to produce DILP8. In this case, the counterpart of this organ responds to DILP8 and slows down its growth as well as delaying the timing of metamorphosis. This delay is necessary for the abnormally developing organ to catch up with the counterpart. If DILP8-Lgr3 signaling is compromised, the abnormally growing organ fails to alter developmental timing and ends up being either smaller or larger than its counterpart, which exhibits the expected normal size. In normal larval development, the transcription factors of the Hippo pathway, Yorkie and Scalloped, are proposed to regulate the expression of *dilp8* (Boone et al. 2016). The Hippo pathway is known to regulate cell growth and proliferation through changes in cytoskeleton network and cell-to-cell contact (Bosveld et al. 2012; Pan et al. 2016, 2018). As such, this regulation of *dilp8* expression by Hippo pathway transcription factors seems to couple *dilp8*'s functions in regulation of developmental timing and reduction of fluctuating asymmetry. Accordingly, this Hippo signaling-induced *dilp8* expression couples developmental timing and organ growth perturbation by changing the timing of ecdysone secretion via the PTTH-prothoracic gland axis.

3.3 Mediators of Tissue Plasticity

Growth and re-patterning of tissues are regulated by many signaling pathways that modulate cell proliferation and growth. In insects, ecdysteroids, JH and IIS play important roles in regulating tissue growth during adult tissue formation and

morphogenesis. In many species, these endocrine factors are also used to mediate environmental cues. In this section, we review how these factors regulate normal adult tissue formation and morphogenesis.

In many holometabolous insects, adult morphogenesis of most tissues begins during the final larval instar. A handful of structures, such as wing imaginal discs, form during embryogenesis, but these early-forming imaginal discs are thought to be derived traits that arose independently several times within the Holometabola (Svácha 1992; Truman and Riddiford 1999). Growth of the late-forming adult tissues, which consist of several undifferentiated cells and do not proliferate actively until certain developmental stage, begins early in the final instar. In *M. sexta*, for example, leg and eye primordia begin to proliferate soon after the larvae begin to feed (MacWhinnie et al. 2005; Allee et al. 2006; Truman et al. 2006; Truman and Riddiford 2007; Truman 2019). At the onset of the final instar, JH suppresses proliferation. This morphostatic action of JH is nutrient dependent as JH prevents imaginal cells from proliferating only under starvation (Truman et al. 2006; Koyama et al. 2008). Once the larvae start feeding, the IIS pathway can effectively override the morphostatic action of JH and allows imaginal cells to proliferate (MacWhinnie et al. 2005; Koyama et al. 2008). This initial growth does not require inputs from ecdysteroids (Truman et al. 2006).

Later in the instar, ecdysteroids play prominent roles in promoting growth of these imaginal tissues. Studies on lepidopteran imaginal discs have shown that both ecdysteroids and Bombyxin—the lepidopteran insulin-like hormone—are required for disc growth (Nijhout and Grunert 2002; Nijhout et al. 2007). Although Bombyxin has no effect on growth of isolated discs cultured in vitro, it can act synergistically with 20E to promote imaginal disc growth (Nijhout et al. 2007). Interestingly, however, the hormones appear to have distinct effects on individual cells: ecdysteroids stimulate cell proliferation, DNA synthesis, and protein synthesis, whereas insulin promotes growth of each cell and protein synthesis (Nijhout et al. 2018).

The IIS pathway also plays an important role in regulating scaling relationships between tissue size and the whole body size. By modulating the expression of InR expression in various tissues, Shingleton et al. (2005) demonstrated that body size is only affected up to pupariation. In contrast, tissue growth continues to be sensitive to InR post feeding until early pupal development. Furthermore, certain tissues are more sensitive to InR modulation than others. For example, the size of the genitalia is robust to InR modulation, whereas wings are much more sensitive to InR expression (Shingleton et al. 2005). Thus, tissue specific sensitivity to the IIS pathway can lead to exaggerated tissue growth. These differential responses to the IIS pathway are mediated by the expression of FoxO, which is inhibited by the IIS pathway (Tang et al. 2011). Because the IIS pathway is sensitive to nutritional environment, this pathway provides a mechanism by which larval nutrition can impact the adult morphology in a tissue specific manner as discussed below. Finally, the IIS pathway impacts organ size in distinct ways at different levels of the IIS activity. Severe reduction of IIS activity leads to smaller organ sizes through reduction in both cell size and cell number, whereas modest reduction of IIS activity

leads to smaller organ size primarily through a reduction in cell size (Shingleton et al. 2005).

3.4 Tissue Growth Polyphenisms

Many insects produce altered adult morphologies that result from exaggerated tissue growth during metamorphosis. Phenotypic plasticity of trait sizes can manifest in two different ways: the scaling relationship between the trait size and the body size can be linear or discontinuous (Emlen and Nijhout 2000). In some cases, exaggerated traits can scale linearly and serve as an honest signal for the quality of mates. Size of horns of some beetle species, such as the rhinoceros beetle *Trypoxylus dichotomus,* and eyestalk lengths of stalk-eyed flies (Diopsidae) are influenced by larval nutrition and can scale linearly with body size (David et al. 1998; Knell et al. 1999; Johns et al. 2014). In contrast, when the scaling relationship is discontinuous such that two or more *distinct* trait size classes are observed, the trait is said to be polyphenic. Such polyphenisms typically exhibit a reduction or absence of the trait at smaller body sizes and a large trait size at larger body sizes. These alternative morphologies often represent adaptations to alternative reproductive strategies, such as male–male combat vs sneaking (Gross 1996).

Local tissue growth can be broken down into two components, growth and patterning. Certain regulators, such as hormones, impact whole tissue growth by promoting overall tissue growth (Koyama et al. 2013). In contrast, local tissue patterning is often a consequence of both endocrine factors and local growth factors, such as morphogens, that promote growth and proliferation within a particular tissue. Some of these environmentally sensitive adult traits develop from cells that begin to proliferate at the end of the larval stage. A classic example is the dung beetle horn, which is absent from the larval body. In these cases, cells within the larval epidermis become specified to form the adult trait. Such specification is typically regulated by hormones, presumably through the influence of JH and/or ecdysteroids. Environmental conditions can impact these hormones and affect the trait specification process. Thus, adults may lack the trait altogether under certain endocrine conditions (Fig. 3.6).

Other traits develop from existing larval structures and become exaggerated during metamorphosis. For example, the impressively large stag beetle mandibles arise from dramatic growth of the modest larval mandibles. Again, endocrine factors play a role in regulating the growth of these structures. Because the initial specification and differentiation step has already occurred during the embryonic stage, the adults will always have a set of mandibles; however, the amount of growth that occurs during metamorphosis is dependent upon the larval environmental inputs.

Below, we discuss several examples of developmental plasticity during metamorphosis and discuss both the adaptive significance of these traits and the developmental basis of these tissue size polyphenisms. We have grouped them according to the scaling relationship between the size of the trait and body size. In some cases,

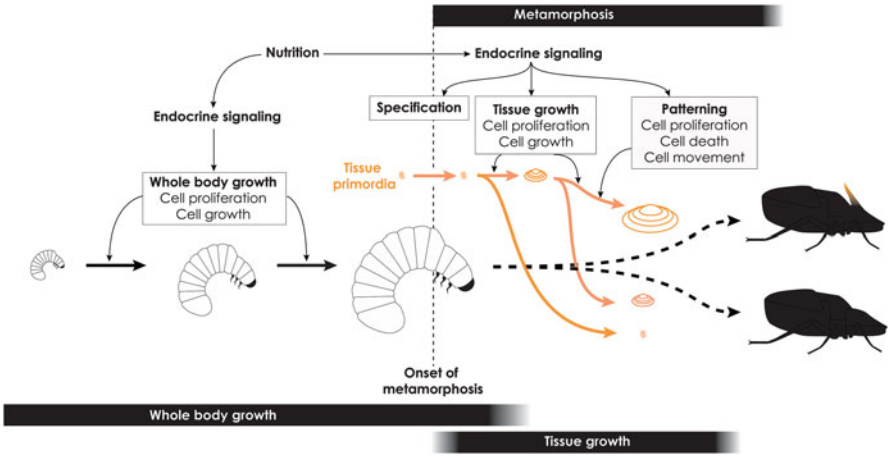

Fig. 3.6 Regulation of tissue allometry. Nutrition impacts both whole body growth and tissue specific growth by modulating the endocrine system. Whole body growth phase: During the feeding period, these endocrine signals primarily regulate whole body growth by stimulating cell proliferation and growth. Tissue growth phase: During metamorphosis, either overlapping or distinct sets of endocrine signals regulate (1) the specification of adult tissues, (2) the localized proliferation and growth of these tissues, and (3) the patterning of these tissues. In some cases, different environmental inputs can modulate these processes to generate divergent adult phenotypes

the relationship is sigmoidal, such that there is a discontinuous scaling relationship between the trait and body size (Fig. 3.7b right). In other cases, the trait scales linearly with body size (Fig. 3.7b, left). Finally, in other cases, the trait size can be influenced by the environment independently of the whole body size such that the alternative morphs do not depend on body size (Fig. 3.7c). We have grouped this latter case under the category of insects that have overlapping allometries.

3.4.1 Insects that Exhibit Sigmoidal Allometries

3.4.1.1 Adaptive Significance

Many dung beetle species have evolved horns on either the head or the thorax (Emlen 2008). In some species, these horns serve as weapons in male–male competition for courtship and thus are often present only on males although females of some species also have horns (Moczek and Emlen 2000; Emlen 2008). However, not all males have horns: small males lack these structures, whereas males above a certain threshold size have large horns (Emlen 1997b). As it turns out, not having horns is not a bad thing: small males can often "sneak" by the larger males and mate with females (Emlen 1997a; Moczek and Emlen 2000). Because small males are favored to have no horns whereas large males are favored to have large horns, these

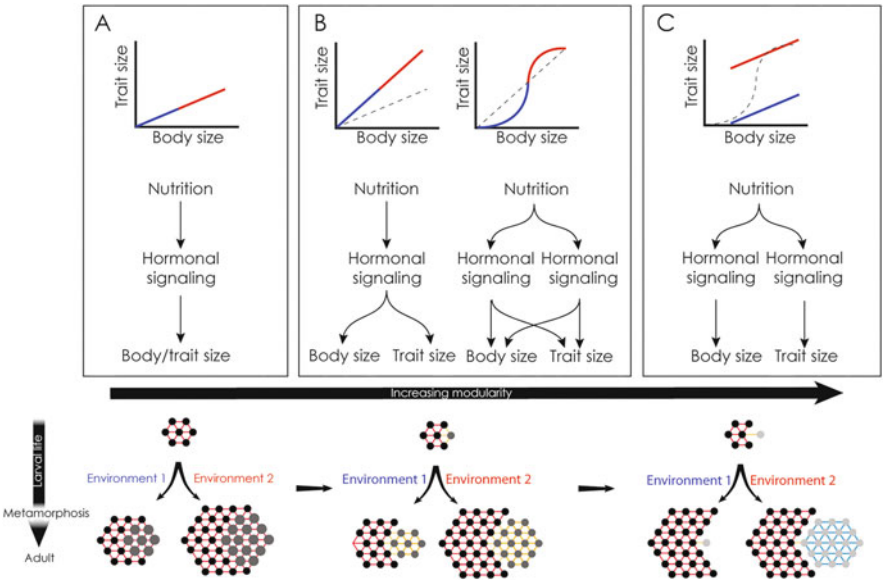

Fig. 3.7 Modularization of tissues facilitates increased uncoupling of trait sizes from body growth. Top row shows the scaling relationship between trait size and whole body size. Middle row shows potential underlying mechanisms that give rise to the particular scaling relationship. Bottom row shows the growth of a hypothetical organism with the cells indicated by dots. The connections between these circles reflect the degree of integration. (**a**) Without modularization, the trait size (gray dots) will scale with the size of the rest of the body (black dots). In this case, the same endocrine signal regulates the growth of the body and the trait. (**b**) In the earliest stages of adult tissue modularization, tissue growth becomes exaggerated with respect to the growth of the rest of the body. Often the sizes of these traits serve as honest signals for the overall condition of the organism. Whether a linear (**b**, left) or a sigmoidal (**b**, right) scaling relationship is observed depends largely on the complexity of signals that regulate tissue growth. If multiple signaling pathways are used, a sigmoidal allometry emerges. (**c**) As tissues become more developmentally uncoupled from the growth of the whole body, their response to the environment becomes localized and independent of the size of the body. This happens if the growth of the trait and growth of the whole body are independently regulated

two morphs are maintained by selection (Emlen 1997a). Whether the beetles develop horns or not is determined by the amount of maternally provisioned dung balls (Emlen 1994, 1997b; Moczek 1998). Thus, larval diet determines the morph and the reproductive strategy of the adults.

3.4.1.2 Developmental Regulation

Beetle horns can develop either on the thorax or on the head, depending on the species (Emlen 2008). The regulation of head horn polyphenism has been best elucidated in *Onthophagus taurus*. In *O. taurus*, two hormone sensitive periods have been found. One hormone sensitive period occurs during the feeding period and

corresponds to the specification of horns. If ecdysteroids are absent during this stage, cells in the epidermis are specified to form a horn; in the presence of ecdysteroids, cells do not contribute to a horn (Emlen and Nijhout 1999). During this sensitive period, JH also impacts the horn threshold: if JH is high during this sensitive period, the body size at which horns appear shifts to a larger body size (Emlen and Nijhout 2001).

A second hormone sensitive period occurs after the cessation of feeding (Emlen and Nijhout 1999). This is a JH-sensitive period during which topical application of JH leads to the production of large horns in small adults that normally would have had no horns. Thus, JH can rescue horn production even when cells were previously specified to contribute to a hornless phenotype (Emlen and Nijhout 1999). These studies illustrate the importance of the developmental context during which hormones act. JH during the feeding period shifts the threshold size at which horns are induced, whereas once the larvae have ceased feeding, JH promotes the formation of horns.

Given that nutrition impacts horn size, an obvious endocrine signaling that impacts horn size is the IIS pathway. Interestingly, knockdown of InR in *O. taurus* fails to influence the horn size-body size allometry (Casasa and Moczek 2018). Knockdown of *FoxO*, however, leads to a more linear horn size-body size allometry, indicating that FoxO is responsible for the sigmoidal shape of the allometric relationship. Thus, horn growth of *O. taurus* is a complex trait regulated by at least three distinct endocrine signals. Such complex regulation of trait growth likely leads to the sigmoidal shape of the allometries (Fig. 3.7b right). It is worth noting that the role of FoxO is not conserved across all horns. For example, knockdown of *FoxO* has minimal impact on the body-thoracic horn scaling relationship of *O. nigriventris* (Snell-Rood and Moczek 2012).

3.4.2 Insects with Linear Allometries

3.4.2.1 Adaptive Significance

The adult rhinoceros beetles develop spectacular thoracic and head horns that are used for male–male fights and securing mates (Emlen 2008; Johns et al. 2014; McCullough et al. 2014). The size of the horns scales linearly with the body size, providing an honest signal for the quality of the males (Emlen et al. 2012). These horns arise *de novo* during metamorphosis, and the horns exhibit heightened sensitivity to larval nutritional environment, compared to other body parts (Johns et al. 2014). Many other beetle species also exhibit exaggerated mandibles that allow males to engage in combat with conspecific males (Emlen and Nijhout 2000). Like the rhinoceros beetle horns, these mandibles scale linearly with body size and serve as reliable signals of the larval nutritional status. Although these dramatically enlarged mandibles develop from pre-existing mandibles, the exaggerated growth occurs during metamorphosis and reflects the amount of food a larva was able to

assimilate. Thus, in all of these examples, larval nutritional environment influences adult reproductive fitness.

3.4.2.2 Developmental Regulation

The rhinoceros beetles have exaggerated horns that scale hyperallometrically with body size. In contrast to dung beetles where knockdown of InR has no influence on horn size allometry (Casasa and Moczek 2018), horns of the rhinoceros beetle *Trypoxylus dichotomus* are regulated directly by InR: removal of InR leads to a drastic reduction of horn sizes (Emlen et al. 2012). Because IIS responds directly to nutrients, it is thought that the heightened sensitivity of the horns to insulin provides an honest and exaggerated reflection of the amount of nutrition the larvae had consumed (Emlen et al. 2012). Moreover, JH does not appear to play a major role in regulating the scaling relationship between horns and body size of *T. dichotomus* (Zinna et al. 2016).

The males of broad-horned flour beetle *Gnatocerus cornutus* also exhibit hyperallometry: the males have disproportionately large mandibles as weapons for male–male combat (Okada et al. 2006). The exaggerated growth of mandibles is also mediated by IIS pathway. The expression of one of the *ILP* genes, *ILP2*, in the fat body correlates with the size of the larvae and its knockdown leads to a clear reduction in mandible size, leading to an isometric relationship between mandibular and body sizes (Okada et al. 2019). In contrast, topical application of the JH analog leads to the enlargement of the mandibles as well as the head and the prothorax (Okada et al. 2012). Whether or not nutritional status influences the size of the mandibles in this species is not known.

In the stag beetle *Cyclommatus metallifer*, the mandible size depends on the body size. In this species, however, JH also plays a prominent role in regulating the size of the mandibles. The JH-sensitive period in the post-feeding period determines the size of the mandibles: males with higher JH titers grow larger mandibles (Gotoh et al. 2011, 2014). Whether or not IIS plays a role in regulating the size of mandibles in this species is not known.

A comparison of the processes underlying the development of exaggerated traits demonstrates that although hormones are always involved, they have distinct effects on the final adult morphology. When adult traits and body size are regulated by the same hormonal signals, the scaling relationship is likely to be linear (Fig. 3.7b, left). Differential expression of receptors/timing of sensitive periods, or changes in the downstream effectors, can alter the slope of these linear scaling relationships. In contrast, when more than one hormonal mechanism influences body and trait size in different ways, the scaling relationships can adopt a more sigmoidal shape (Fig. 3.7b, right).

3.4.3 Insects with Overlapping Allometries

3.4.3.1 Adaptive Significance

Species exhibiting wing length polyphenism can have fully formed wings (macropter or alate) or develop into flightless morphs, with reduced wings (brachypter) or no wings (apter). The persistence of the two morphs reflects trade-offs associated with flight capability and reproduction. Macropterous insects have reduced reproductive outputs relative to brachypterous insects because of energetic costs necessary to construct and maintain wings and flight muscles (Roff 1986). More research needs to be conducted on male specific fitness costs (mate detection, attractiveness, etc.), but orthopteran and planthopper macropters appear to be less fecund than their flightless counterparts (Roff 1986; Zera and Denno 1997). The fully functional macropterous forms, however, can escape deteriorating environments and colonize new areas with their flight-capabilities (Roff 1986; Denno et al. 1991; Zera and Denno 1997). Thus, the production of macropters is typically density-dependent and further induced by insufficient or inadequate resources although this is certainly not the rule. For example, in a few cricket species, brachypters develop when they lack resources necessary for macropter production (Zera and Denno 1997).

3.4.3.2 Developmental Regulation

Wing polyphenisms are influenced by exposure to various environmental cues, such as population density, host plant condition, temperature, and photoperiod during the nymphal stages (Denno and Roderick 1990; Zera and Denno 1997). JH signaling, ecdysteroid signaling, and IIS pathways appear to respond to these cues and influence the growth of wings. In the crickets and planthoppers, topical application of JH and removal of JH leads to higher proportion of brachypters and chemical ablation of the corpora allata, the source of JH, leads to higher proportion of macropters (Iwanaga and Tojo 1986; Zera and Tiebel 1988; Ayoade et al. 1996). Moreover, in the migratory planthopper *Nilaparvata lugens,* reduction in the expression of gene encoding a JH degradation enzyme, *JH epoxide hydrolase,* causes the formation of brachyperous morphs in a predominantly macropterous strain (Zhao et al. 2017). In *G. rubens,* the activity of another JH degradation enzyme, JH esterase (JHE), is elevated in the presumptive macropterous nymphs. Subsequent studies on artificially selected lines of *G. firmus* demonstrated that crickets selected for longer wings have elevated levels of JHE compared to those selected for shorter wings (Zera and Huang 1999). Although direct evidence of the role of ecdysteroids on wing dimorphism is lacking, presumptive brachypterous morphs have lower ecdysteroid titers during the wing morph determination period compared to the presumptive macropterous nymphs (Zera et al. 1989). Recent studies have demonstrated that the IIS pathway plays a critical role in the determination of wing morphs of *N. lugens*. The two

insulin receptors identified in this species appear to play antagonistic roles: InR1 is necessary for macropter development, whereas knockdown of *InR2* leads to macropter development. InR1 appears to act in the canonical IIS pathway, while InR2 acts to antagonize the canonical IIS (Xu et al. 2015). These studies demonstrate that JH signaling, ecdysteroid signaling, and IIS are involved in regulating wing growth.

3.4.4 Modularity Facilitates Environmental Sensitivity of Trait Sizes

As discussed above, polyphenisms are regulated by tissue specific responses to endocrine regulators. Developmental modularity of these tissues facilitates the localized fine-tuning of adult morphogenesis and patterning during metamorphosis. At the molecular level, developmental plasticity of tissues can arise as a consequence of (1) changes in the number of local receptors, (2) heterochronic shifts in the timing of receptors, or (3) expression of a unique set of endocrine response genes. Depending on the degree of developmental dissociation of the trait from the rest of the organism, the trait may reflect the size and condition of the body. Some traits are developmentally integrated with the whole body and can serve as an honest signal of the organism's overall condition and fitness at the time of metamorphosis (Fig. 3.7a, bottom row). In other cases, the trait development may barely reflect the condition of body (Fig. 3.7c, bottom row). These differences reflect the degree to which the trait undergoes morphogenesis independently of the rest of the body.

3.4.5 Butterfly Color Polyphenisms

We end our discussion with size-independent polyphenisms, specifically focusing on butterfly wing color polyphenisms because it has been well documented. A discussion of how larval environment impacts adult fitness would be incomplete without exploring its role and effects in butterflies.

3.4.5.1 Adaptive Significance

Seasonal polyphenisms of butterfly wings include some of the most spectacular examples of polyphenisms. Many species of butterflies belonging to the family Nymphalidae show wing color polyphenisms in which the coloration of the entire wing or the size of eyespots can respond in an environmentally sensitive manner. For example, in the European map butterfly, *Araschnia levana*, the wings of the summer morph are mostly black with a white band whereas the spring morph is

mostly red with disjointed black bands. These alternative morphs arise as a consequence of the photoperiod and temperature that the larvae experience (Koch and Bückmann 1987). It has been proposed that the black summer form is a derived morph that arose in response to selection for crypsis whereas the red ancestral morph may advertise their distastefulness or mimic other distasteful species (Fric et al. 2004).

Butterfly eyespots originally evolved as 4–5 units on the ventral hindwings and were later co-opted onto forewing and dorsal wing surfaces (Oliver et al. 2012). Numerous proposals for the functions of eyespots on butterflies center around predator–prey interactions or sexual signaling (Kodandaramaiah 2011; Monteiro 2015). The deflection hypothesis suggests that eyespots deflect attacks to non-vital body parts by capturing the attention of predators to the wing margin. According to the intimidation hypothesis, large eyespots that consist of vibrant colors may imitate eyes that serve to deter predators (Ho et al. 2016). In some species, eyespots appear to be involved in sexual selection. For example, *Bicyclus anynana* appear to have a preference for mates with UV-reflective eyespot "pupils" found in larger eyespots (Robertson and Monteiro, 2005; Prudic et al. 2011).

In the Nymphalidae family, many species have ventral eyespots that express adaptive phenotypic plasticity in response to their environment (Brakefield and Larsen 1984). For instance, *B. anynana* in hot/wet seasons have conspicuous ventral eyespots and a transverse band, while in cool/dry seasons, they have small eyespots with no band (Brakefield et al. 1998; Windig et al. 1994). The large eyespots of the hot/wet-season morph help deflect attacks of invertebrate predators, or naive vertebrate predators toward the wing margins, whereas the reduced eyespots of the cool/dry-season morph are thought to be helpful with camouflage against predation (Lyytinen et al. 2004).

3.4.5.2 Developmental Regulation

Wing color polyphenism described above are all regulated by fluctuating titers of ecdysteroids. In *A. levana*, the coloration of the wings is dependent upon the presence of 20E during the pupal sensitive period (Koch and Bückmann 1987). Although only two morphs are observed, injection of 20E or intermediate environmental conditions can lead to the development of intermediate morphs (Nijhout 2003b). Similarly, wing color polyphenisms of the common buckeye butterfly, *Junonia coenia* is also dependent upon ecdysteroid levels during the pupal sensitive period (Rountree and Nijhout 1995). When larvae develop under short day/cool conditions, reddish brown wings develop as a consequence of having low circulating levels of ecdysteroids. In contrast, when larvae develop at longer/higher temperatures, the ecdysteroid levels are elevated and a light brown morph develops (Rountree and Nijhout 1995).

The size of the eyespots in *B. anynana* is also regulated by 20E titers. During the wandering stages of larval development, 20E titers are higher in larvae reared at a high rearing temperature (leading to the wet-season morph) than those reared at a

low temperature (leading to the dry-season morph) (Monteiro 2015). This elevated 20E titer is accompanied by increased expression of the Ecdysone receptor, EcR, in the presumptive eyespots of wing discs (Monteiro et al. 2015). Injections of 20E into early pupae of the cool dry-season form yield butterflies with enlarged ventral eyespots, similar to that of the hot wet-season form (Brakefield et al. 1998).

3.4.6 *Impact of Juvenile Immune Activation on Adult Phenotypes*

In insects, similarly to other organisms, the activation of an immune response is a costly process that requires the allocation of energy resources (Lochmiller and Deerenberg 2000; Read and Allen 2000; Ardia et al. 2012). In fact, the outcome of an infection depends on the ability of an organism to deviate resources from other biological processes, such as growth and reproduction, to fuel an immune response (Eisenreich et al. 2013; Galenza et al. 2016). Contrary to vertebrates, where the balance between metabolism and the immune response depends on a complex communication between different organs devoted to either immunity or energy storage, in insects these two processes are centralized in the fat body (Arrese and Soulages 2010). In *D. melanogaster,* the transcription factor MEF2 was shown to be involved in the coordination of immunity and metabolism in the fat body (Clark et al. 2013). Under conditions of high nutrition availability and in the absence of pathogen exposure, MEF2 promotes lipogenesis and glycogenesis. However, when flies are infected, MEF2 is unphosphorylated and shifts the fat body activity from energy storage to the release of antimicrobial peptides (AMPs) (Clark et al. 2013).

ILPs are one of the most important regulators of growth and metabolism (Gronke et al. 2010; Gronke and Partridge 2010). Because the immune response has an impact on energy stores, an association between these hormones and the immune system would be predictable. In fact, in *D. melanogaster*, infection with the intracellular bacterial pathogen *Mycobacterium marinum*, leads to decreased Akt activation, facilitating the expression of the negative regulator of the IIS pathway, FoxO (Dionne et al. 2006). This results in a consequent progressive loss of energy stores and higher mortality due to the lack of energetic resources to fuel the immune response (Dionne et al. 2006). This was the first time the IIS pathway and immunity were connected in insects although direct evidence that the immune system impacts growth came later. In insects, sensing of microbe associated patterns leads to the activation of two canonical pathways: Toll or Imd (Lemaitre and Hoffmann 2007). DiAngelo demonstrated that activation of the Toll in the larval fat body suppresses IIS, leading to a reduction in body size and a developmental delay (DiAngelo et al. 2009). Later it was demonstrated that activation of Toll signaling impacts IIS activation by targeting DILP6 (Suzawa et al. 2019) and causing the inhibition of Akt by PDK1 (Roth et al. 2018). As such, the reduction of growth caused by Toll signaling activation can be rescued by restoring Akt activity locally in the larval fat

body or by restoring DILP6 levels (Roth et al. 2018; Suzawa et al. 2019). This reduction in larval growth further impacts adult life, as reduced IIS caused by Toll activation in the larval fat body results in adults with smaller wing size (Suzawa et al. 2019).

Besides affecting adult size through interaction with the IIS, activation of the immune system during juvenile stages also impacts traits such as behavior, reproductive investment, and adult immunity. In the field crickets, *Gryllus integer*, exposure to pathogens during early juvenile stages influenced the lack of repeatability of boldness/aggressive behaviors in the adult stage, as measured by the insect's willingness to be exposed in a novel environment (DiRienzo et al. 2015). This might be because early pathogen exposure predicts future environmental instability, in which higher behavioral plasticity would be advantageous (DiRienzo et al. 2015). In another species of field crickets, *Teleogryllus oceanicus*, males with restricted access to food and that are exposed to pathogens prior to maturity face a resource allocation trade-off, decreasing sperm quality in the adult stage (Simmons 2011). This decreased investment in reproduction after an immune challenge has been thoroughly described (Folstad and Karter 1992) and, in insects, this is generally accepted to be the consequence of the association between JH and immunity (Schwenke et al. 2016; Schwenke and Lazzaro 2017; Nunes et al. 2020). However, in none of these cases was the immune response of the adults influenced by the early activation of immunity (Simmons 2011; DiRienzo et al. 2015). Studies on *Gryllus campestris* demonstrated that injection of lipopolysaccharide, a component of bacterial cell walls, into nymphs led to increased hemolymph bactericidal activity, as well as an increased expression of prophenoloxidase in adult crickets, which suggests this long-term induction of immunity as a strategy to deal with future infections (Jacot et al. 2005). Importantly, this sustained immune activity until adulthood comes at a cost, resulting in a lasting reduction in metabolic function, as seen by reduced hemolymph protein concentration that can have further impacts on host's fitness (Jacot et al. 2005).

In summary, immune activation and pathogen exposure during immature stages in insects impacts growth, generating smaller adults. Furthermore, in some cases, this can also be reflected on other aspects of adult life, such as reproduction and behavior that can impact the insect's adaptation to novel environments and conditions of scarcity.

3.5 Conclusions

Environmental influences during the immature stage have major influences on adult phenotypes. Metamorphosis facilitates the adaptive fine-tuning of the adult phenotypes by uncoupling the development of juvenile and adult stages. Thus, modularization of life history stages offers ways to integrate environmental cue and alter adult phenotypes in adaptive ways. Moreover, we see that developmental modularity facilitates the evolution of polyphenisms. Because developmental

plasticity is thought to promote phenotypic diversification, adaptation and speciation (West-Eberhard 2003, 2005), studies on how organisms' juvenile experience impacts adult phenotypes will have important consequences for understanding how organisms evolve in changing environments.

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Part II
Endogenous Mechanisms Underlying the Interactions Between the Individual and Its Early-Life Environment

Chapter 4
Early-Life Stress Drives the Molecular Mechanisms Shaping the Adult Phenotype

Susanne Huber, David Costantini, Cecilia Houdelier, and Valeria Marasco

Abstract Exposure to challenging experiences during development, such as reduced parental care and food availability, can have profound effects on the adult phenotype with far-ranging consequences for individual performance. Traditionally, such early-life adversities have been assumed to lead to detrimental consequences for health and survival. Growing empirical evidence, however, pin point that early-life stress exposure can also promote adaptive coping mechanisms of resistance and resilience, and have beneficial long-lasting effects. Developmental timing, type, and severity of early-life stress exposure are hypothesized to be key features underlying subsequent phenotypic outcomes. In this book chapter, we provide an overview of the main molecular mechanisms and signals that may be driving the emergence of subsequent stress vulnerability or resilience. We focus on the actions of glucocorticoid hormones in shaping adult physiological stress responses, and in organizing key cellular and molecular mechanisms underlying senescence and life-history evolution, including telomeres, oxidative stress, and epigenetics. Finally, we critically appraise and identify gaps in our current knowledge and provide directions for future research.

S. Huber
Department of Evolutionary Anthropology, University of Vienna, Vienna, Austria

D. Costantini
Unité Physiologie Moléculaire et Adaptation, UMR 7221, Muséum National d'Histoire Naturelle, CNRS, CP32, Paris, France

C. Houdelier
Ethologie animale et humaine, Universities of Rennes 1 and Caen-Normandie, CNRS, Rennes, France

V. Marasco (✉)
Konrad Lorenz Institute of Ethology, University of Veterinary Medicine Vienna, Vienna, Austria
e-mail: Valeria.Marasco@vetmeduni.ac.at

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4.1 Introduction

The responses of an organism to early-life environmental conditions can have long-term effects on morphology, physiology, and behavior, potentially persisting for the whole lifespan and beyond one generation (Monaghan 2008). Organisms are currently exposed to growing environmental pressures including increased urbanization, habitat fragmentation, and climate changes due to global warming (Loarie et al. 2009; Bellard et al. 2012). Understanding how these challenges influence individual's life history trajectories, and over what life stage effects are most likely to result in long-lasting phenotypic changes is a major research priority (Romero et al. 2015; Slavich 2016).

Animals evolved endogenous systems to appropriately respond to stressful conditions and return to homeostasis as fast as possible. In vertebrates, stress responses involve a highly conserved suite of molecular, physiological, and behavioral changes that are essential for promoting immediate survival strategies (Wingfield et al. 1998; Sapolsky 2000). But here the inevitable question—what is "stress"? Hans Selye, the "father of stress," once said, "Everybody knows what stress is, but nobody really knows what it is" (Selye 1973). The scientific definition of "stress" continues to be hotly debated. This is mainly due to the difficulties in rigorously defining the stimuli causing stress exposure ("stressors"), the emergency responses activated by these stimuli, and the pathological consequences associated with overstimulation of the emergency responses (Mcewen and Wingfield 2003; Romero et al. 2009). In this book chapter, we use the term "stress" to broadly refer to the activation of conserved stress response systems, i.e., neuroendocrine, endocrine, and metabolic responses to noxious stimuli, or stressors, to maintain or recover physiological homeostasis. We refer to "early-life stress" to indicate different kinds of challenges or adversities sexually immature/developing individuals might be exposed to, including, but not limited to, nutritional restrictions, limited parental resources, social competition, predation pressures, extreme temperatures, or pollutants (Romero et al. 2015; Sapolsky 2015).

Epidemiological evidence showed substantial links between various forms of early-life stressors, including intrauterine growth restriction, harsh socio-economic conditions, and increased propensity to the emergence of adult-diseased phenotypes (Barker et al. 1990, 1993; Cottrell and Seckl 2009). A notorious example is the study of the long-term effects of the Dutch Hunger winter in 1944–1945 (in which daily rations were limited up to 1000 kilocalories per day). Individuals exposed to the famine during the pre- and peri-natal period had increased risk to develop obesity, diabetes, and coronary heart disease in adulthood (Ravelli et al. 1999; Roseboom et al. 2001; Painter et al. 2005, 2006). Moreover, individuals exposed to prenatal stressors were found to be at increased risk of neurodevelopmental and behavioral health issues, such as depression, schizophrenia, and autism spectrum disorder (Khashan et al. 2008; Kinney et al. 2008; Markham and Koenig 2011). These studies contributed enormously to the foundation of the *Developmental Origins of Health and Disease (DOHaD)" hypothesis* (originally termed "*Fetal Origins of Adult*

Disease"—Hales et al. 1991). DOHaD postulates that adverse conditions experienced during the pre- and early post-natal period lead to subsequent increased morbidity and mortality. There is, however, a growing body of empirical work on a range of taxa, especially within the fields of eco-devo research, suggesting that developmental stress can also result in long-lasting phenotypic adaptations that may promote resilience, thus increase capability to cope with subsequent stressors (reviews: Monaghan 2008; Sih 2011; Langenhof and Komdeur 2018). These studies challenge the predominantly biased negative connotation of early-life stress on fitness outcomes and open empirical plausibility through which certain stressors might optimize individual coping strategies depending on future environmental circumstances (Gluckman et al. 2005, 2007).

We still have a poor understanding of the endogenous mechanisms through which exposure to developmental stress might lead to positive or negative fitness outcomes. Two key aspects in this context are: Which processes embed early-life experiences into molecular changes and signals? Which are the main molecular mechanisms regulating such organizational effects and how do they alter subsequent stress vulnerability and resilience? Endocrine systems are undoubtedly excellent candidates as modulators of developmental plasticity. Hormones influence a large number of processes across the entire lifespan and their pleiotropic effects can mediate variation in life histories. The influence of hormones on phenotypic traits is known to be particularly powerful during early development when they exert organizational effects on physiology or anatomy with long-lasting consequences on subsequent adult behaviors and lifestyles (Arnold 2009; Nugent et al. 2012). Glucocorticoid hormones, controlled by the Hypothalamic–Pituitary–Adrenal (or Interrenal) axis (HPA axis), are key mediators of the vertebrate stress response and fundamental candidates linking coping behaviors to environmental challenges, such as inclement weather and food availability (Sapolsky 1992; de Bruijn and Romero 2018). Thus, changes in the functioning of the HPA axis, for instance through a re-setting of HPA axis sensitivity during ontogeny, are thought to be a key mechanism underlying the links between early-life adversity and long-term health and adult-disease risk (Welberg and Seckl 2001; Seckl 2004; Meaney et al. 2007; Cottrell and Seckl 2009; Harris and Seckl 2011). Although other hormones have also substantial effects on the phenotype programming (e.g., sex steroids and thyroid hormones), we purposely focus on glucocorticoids because (i) we have a larger body of experimental work in both laboratory and wild settings, and (ii) emerging evidence suggests a role of these hormones in organizing important cellular mechanisms underlying senescence and life-history evolution, such as telomere dynamics and oxidative stress (Price et al. 2013; Angelier et al. 2018; Ridout et al. 2018). Telomeres shorten with age in many studied organisms with steep declines often being observed during early development (Heidinger et al. 2012; Angelier et al. 2018). Importantly, telomere length and rates of telomere shortening appear to be in some circumstances good predictors of individual's quality and subsequent longevity (Cawthon et al. 2003; Heidinger et al. 2012; Wilbourn et al. 2018). Moreover, telomeres are influenced by various developmental stressors associated with changes in growth trajectories or parental care (Boonekamp et al. 2014; Marchetto et al. 2016;

Monaghan and Ozanne 2018), and exposure to environmental stressors that cause oxidative stress fosters telomere attrition (Hau et al. 2015; Reichert and Stier 2017; Casagrande and Hau 2019). Thus, telomere length and dynamics have been considered to act as biomarkers of "biological age" and of exposure to environmental challenges. Oxidative stress refers to any changes in cellular oxidative status, which involve oxidation products (oxidative damage), nonenzymatic and enzymatic antioxidants, or repair mechanisms, which may potentially impinge on fitness-related metrics or on molecular mechanisms driving senescence, such as telomere length (Costantini 2019). Measurements of telomere dynamics and oxidative status markers have usually been used to trace the effects of challenging developmental conditions. However, they might also be important modulators of cellular signalling, thus they could potentially orchestrate some of the programming effects of early-life stress.

In this book chapter, we focus on the three inter-linked key endogenous mechanisms that could orchestrate the organizational effects of early-life stress: HPA axis functioning, telomere dynamics and oxidative stress, and epigenetic changes. We focus on mammals and birds in particular due to the larger body of literature, but the mechanisms and theories we discussed are valid across all vertebrate taxa.

4.2 Roles of Developmental System, Timing, and Stressor Type

Early-life stress experiments in animals allow for well-directed environmental manipulations during specific phases of pre- and/or post-natal development. Although the effects of early-life stress are examined in numerous different species including livestock and nonhuman primates (e.g., Abbott et al. 2008; Reynolds et al. 2010), most of the experimental studies use rodents as model systems. This is primarily due to feasibility as rodents are easy to house and handle together with much lower costs compared to primates.

As mammals depend upon the mother during prenatal development and also need intensive postnatal maternal care for normal development, early-life stress paradigms are typically based upon manipulations of maternal physiology and behavior. By cross-fostering of pups to control mothers or nursery rear it can be established whether the found effects are caused by particular pre- and/or postnatal events (Glover et al. 2010). In prenatal models, maternal stress or glucocorticoid administration is transferred via the placenta from mother to the developing fetus (Seckl 2001). In rats and mice, prenatal stress is typically imposed by restraint of the pregnant dam or administration of exogenous glucocorticoids during pregnancy. The mother is the key figure of early postnatal development in mammals as well. In postnatal stress models, stress experienced by the offspring is typically caused by manipulations of maternal behavior. In rodents, for instance, maternal care not only involves lactation but also offering of an adequate nest and specific behaviors, such

as nursing, licking, and grooming, that provide important sensory input to the pups. Postnatal stress paradigms therefore most often involve prevention or disturbance of maternal care via temporary maternal separation from the offspring or allocating the dam with insufficient nesting material. Accordingly, the most common approaches of postnatal stress exposure are the maternal separation model and providing limiting nesting material. Importantly, maternal separation protocols vary greatly among studies depending on the frequency and duration of the separation episode as well as the specific age for separation. A review on the different experimental maternal separation protocols is beyond the scope of the present chapter. However, as a general rule, the greater is the frequency and duration of the separation episodes the greater the severity of the stress exposure (Parker and Maestripieri 2011).

More recently, birds have been employed as study systems to assess how early-life stress shapes an individual's life history strategy within different eco-physiological contexts. Being egg-laying species, they offer the possibility to experimentally tease out pre- versus post-natal effects. In addition the reduced physiological intimacy between the developing bird and the mother as compared to mammals allows minimizing potential compensatory effects of the parents on the growing offspring (Love and Williams 2008; Spencer et al. 2009; Henriksen et al. 2011; Schoech et al. 2011; Marasco et al. 2012; Zimmer et al. 2013). One of the mostly used prenatal stress paradigms in birds is direct glucocorticoid injection in the yolk of the fertile egg soon after laying. Work in different species found that maternally derived yolk glucocorticoids reflect female condition and the environment to which females are exposed to at reproduction and during egg formation (Hayward and Wingfield 2004; Saino et al. 2005). Postnatal stress paradigms in the avian literature are in general more varied than in mammalian models. Apart from direct glucocorticoid treatment that is generally accomplished through oral dosing (Spencer et al. 2009), implants (Hayward and Wingfield 2004), or dermal patches (Wada and Breuner 2008), researchers have also used manipulations of brood size, sibling competition, ectoparasites exposure, predator cues, and food availability (reviewed by Schoech et al. 2011; Crino and Breuner 2015) as a way to increase stress levels in a developing bird within ecologically relevant contexts. Importantly, in highly precocial birds, such as domestic chickens and quails in which eggs are artificially incubated in the lab and no maternal care is provided to the chicks, the effects of postnatal stressors can be assessed excluding the possibility that parents would compensate for them as known to happen in rodent models.

Early stress paradigms are various, using different types of stressors with different intensity/duration and at different developmental stages. In this context, the comparisons of stress effects using direct hormonal administration of glucocorticoids or indirect manipulations of developmental stress exposure (e.g., changes in food availability and/or parental care) are often discussed. As argued in Crino and Breuner (2015), direct glucocorticoid treatment offers high control of the amount of stress applied and influences one component of a complex internal system. On the other side, indirect manipulations offer less experimental control as they alter multiple components of a complex pathway (regulation of energy availability) but are likely to be a better representation of naturally relevant conditions. For example,

as a direct glucocorticoid injection in the yolk, exposing laying females to environmental stressors can induce an increase of corticosterone levels in their eggs, but higher variations among differing egg hormonal contents can also occur in relation to individual sensitivity of females to stressors or the matching between stressor timing and egg formation (Henriksen et al. 2011). However, when using indirect paradigms, other egg components could be modulated by the individual stress levels of the females, including yolk androgens/gestagens levels or albumin/yolk mass that influence embryo's development and take part in the general mechanisms involved in prenatal programming effects (Guibert et al. 2011; Henriksen et al. 2011). Today, direct and indirect stress protocols are considered complementary methods, each one exploring different facets of early-stress processes. Comparing and interpreting results from studies that used direct versus indirect manipulations of stress exposure are useful but not straightforward due to multiple factors differing among them, including species and population life-histories, housing conditions, duration/intensity/timing of the specific stress paradigms. Despite not always possible, performing studies exploring the phenotypic effects induced by different stressor types can improve result interpretation (Crino and Breuner 2015).

The developmental timing in which stress exposure is experienced is another determining factor for its long-term effects. In their recent review, Berghänel et al. (2017), for instance, showed that the timing of prenatal maternal stress across mammal species determines growth trajectories in the offspring. Only if offspring were exposed to prenatal stress early in pregnancy, accelerated growth patterns probably as part of a faster life history strategy have been found (e.g., Dmitriew 2011; Schöpper et al. 2012; Berghänel et al. 2016), whereas prenatal stress in later pregnancy was rather associated with reduced pre- and post-natal growth (e.g., Merlot et al. 2013; Rooke et al. 2015). In addition, it has often been reported that prenatal stressors lead to different effects on stress physiology, brain, and behavior compared to postnatal stressors (e.g., Macri and Wuerbel 2006; Lupien et al. 2009; Marasco et al. 2012, 2016; Zimmer et al. 2013; Andersen 2015). The stage in which stress exposure occurs is tightly interconnected with the severity of adversity and the degree of development at birth. It is generally held that the earlier stress exposure takes place and/or the longer its duration, the more severe would be its long-term phenotypic consequences (Lindstrom 1999; Monaghan 2008; Lupien et al. 2009; Danese and McEwen 2012). For example, in the Japanese quail exposure to prenatal stress had stronger effects than postnatal stress in terms of long-term changes in physiological stress reactivity and stress-related behaviors (Zimmer et al. 2013, 2017), as well as transcriptome profiles in the brain (Marasco et al. 2016). However, postnatal stressors can also lead to long-lasting phenotypic changes in various species, both birds and mammals (e.g., Liu et al. 1997; Spencer and Verhulst 2007; Banerjee et al. 2012). These contrasting effects may be explained by interspecies temporal differences in the brain development along the precocial-altricial spectrum. In precocial species that produce relatively mature offspring at birth/hatching, maximal brain growth, and neuroendocrine maturation take place in utero/ovo. By contrast, in altricial species producing immature offspring at birth/hatching, brain developmental processes are comparatively delayed with substantial

brain growth occurring during postnatal developmental stages. In addition, in line with the "developmental hypothesis" (Schwabl 1999), the timecourse of HPA axis responsiveness can markedly differ depending on the mode of development, thus on the capacity of the young animal to cope with and avoid stressors across the different stages of postnatal growth. For instance, in several studied bird and mammalian species, adrenocortical capacity to respond to stressors develops much earlier in precocial juveniles compared to altricial juveniles (reviewed by Brown and Spencer 2013).

4.3 Potential Life-Long Mechanisms of Early-Life Stress for Adverse or Positive Organismal Outcomes

4.3.1 Reprogramming of the HPA Axis

Glucocorticoid hormones, controlled by the Hypothalamic–Pituitary–Adrenal axis (HPA axis), are one of the major components of the stress response (Sapolsky 1992; Stratakis and Chrousos 1995; Wingfield et al. 1998; Sapolsky et al. 2000)—see Box 4.1 for a description of the principal systems regulating the stress response. Contrary to adrenaline and noradrenaline, glucocorticoids can easily cross the blood–brain barrier and bind to corticosteroid receptors in the brain (mainly glucocorticoid receptors and mineralocorticoid receptors) to influence brain function and cellular energetic signalling (Reul and Dekloet 1985; Datson et al. 2001). Hence, glucocorticoid hormones are thought to be ideal candidates for mediating the long-lasting changes of early-life stress.

Box 4.1 The Stress Response

All vertebrate species elicit highly conserved, relatively nonspecific, behavioral, and physiological changes upon exposure to stressors. Within seconds to hours upon the perception of stressful cues, two endocrine systems are activated, one involving catecholamines, such as adrenaline (acting within seconds) from the adrenal medulla, and the other involving glucocorticoids (acting within minutes) secreted from the adrenal cortex (Stratakis and Chrousos 1995). The fastest component of the stress response, best known as the "fight or flight response" triggers a variety of physiological changes, including increased cardiovascular tone and respiration rate prompting the body for immediate reactions and muscular action (Cannon 1929). As shown in the Fig. 4.1, within minutes upon perception of a stressor, two neuropeptides from the paraventricular nucleus of the hypothalamus, corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), act synergistically to stimulate the secretion of adrenocorticotropic hormone (ACTH) from corticotroph cells in the anterior pituitary gland. ACTH is then transported

(continued)

Box 4.1 (continued)
via the systemic circulation to the adrenal cortex, where it stimulates the production and secretion of glucocorticoids (corticosterone in majority of amphibians, reptiles, and birds, and cortisol in majority of mammals—Harvey et al. 1984). The increased glucocorticoids in the circulation initiate an array of metabolic and behavioral effects that stimulate hepatic gluconeogenesis, inhibit glucose uptake by peripheral tissues and suppress inflammation and several immune reactions to maintain body homeostasis (Munck et al. 1984). The HPA axis is tightly regulated over time via negative feedback loops (indicated in the figure below by the sign −) on mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) in the brain and anterior pituitary. Under acute stress conditions, feedback mechanisms operate efficiently and the effects of elevated glucocorticoids are only short-term (within hours). In the brain, MR have a higher affinity than GR for glucocorticoids. Therefore, at basal concentrations of glucocorticoids, MR are occupied whereas GR remain largely unoccupied. During acute stress, there is increased occupation of GR. Hippocampal and hypothalamic MR are thought to be primarily involved in feedback regulation during basal secretion, while GR become important during stressful conditions (de Kloet et al. 1998; Matthews 2002; McEwen 2007). Under chronic stressful conditions, feedback mechanisms are impaired causing prolonged activation of the HPA axis, with potential detrimental consequences on brain functioning and body processes (Sapolsky 1996). Chronic stress may also reduce activity of the HPA axis under given circumstances. For example, chronically stressed female starlings had lower baseline corticosterone concentrations and lower reproductive success than unstressed females (Cyr and Romero 2007).

Substantial body of work shows that a variety of adversities are consistently associated with long-lasting changes in the functioning of the HPA axis and long-term health diseases (Welberg and Seckl 2001; Seckl 2004; Meaney et al. 2007; Cottrell and Seckl 2009; Harris and Seckl 2011). The general assumption is that early-life stress leads to a hyper-responsive stress phenotype with exaggerated circulating glucocorticoids, enhanced anxiety, and depression-like behaviors (reviews: Maniam et al. 2014; Agorastos et al. 2019). For instance, studies in rodents reported reduced glucocorticoid receptor levels in the hippocampus, attenuated negative feedback, and increased glucocorticoid response to stress in terms of both peak levels and duration of the response (Henry et al. 1994; Barbazanges et al. 1996; Szuran et al. 2000; Green et al. 2011; Bingham et al. 2013). Studies in rats and primates further showed that high glucocorticoid exposure during prenatal life caused elevated basal glucocorticoid levels later in life (Levitt et al. 1996; Welberg et al. 2001; de Vries et al. 2007) although other studies found unaffected basal glucocorticoid levels (review: van Bodegom et al. 2017). Increased adult stress reactivity in response to different stress-related treatments have also been

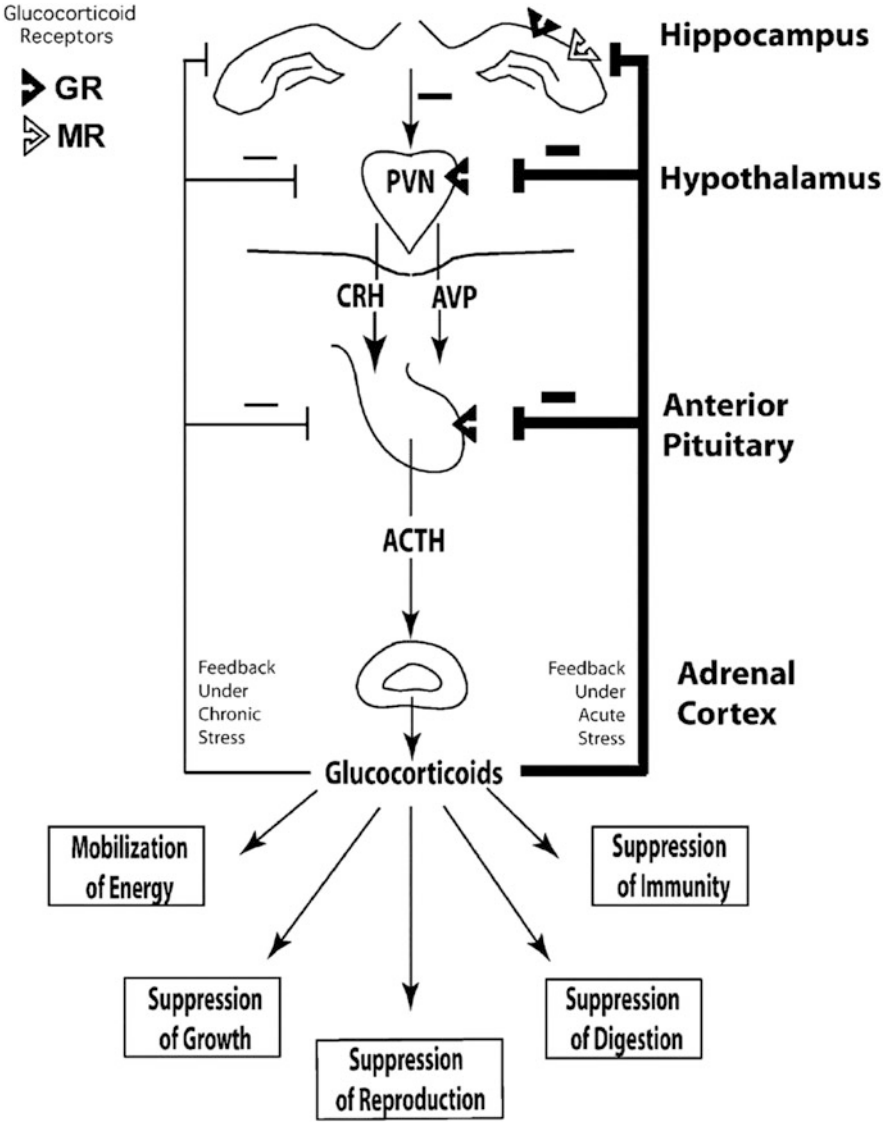

Fig. 4.1 Hypothalamic–Pituitary–Adrenal (HPA) axis. Figure reproduced from Boonstra (2004) with permission of Oxford University Press

experimentally demonstrated in some studied bird species, such as captive zebra finches, domestic chickens, and Japanese quails (e.g., Hayward and Wingfield 2004; Spencer et al. 2009; Banerjee et al. 2012; Haussmann et al. 2012) though, as in mammals, results are quite variable (Henriksen et al. 2011).

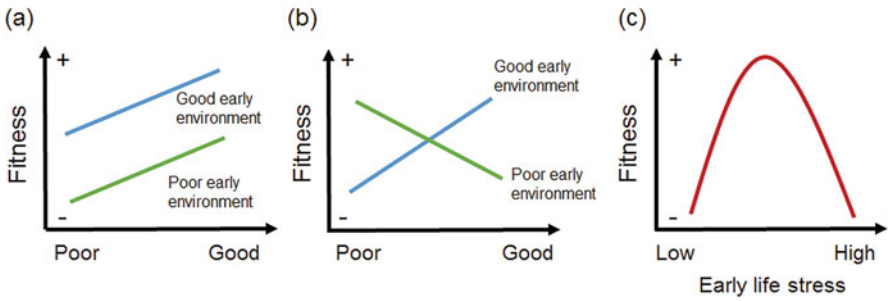

Fig. 4.2 Diagram of (**a**) silver spoon, (**b**) environmental matching, and (**c**) inoculation models. Panels **a** and **b** are redrawn from Pigeon et al. (2019)

It has been suggested that early-life adversity merely constraints development and leads to underperforming adult phenotypes whatever the environmental conditions. In ecological studies, this idea refers to the "silver spoon hypothesis" (Grafen 1988; van de Pol and Verhulst 2006; Monaghan 2008;—Fig. 4.2a). In support of this hypothesis, there are studies conducted in various species including mammals and birds highlighting associations between early-life adversities and reduced fitness-related proxies, including shortened lifespans and reduced reproductive performance (Metcalfe and Monaghan 2001; Spencer et al. 2010; Monaghan et al. 2012; Tung et al. 2016). Could we then conclude that the optimal early-life experience should always be one of low stress exposure? Researchers noted, to their surprise, that exposure to early-life stress can at times, or for some individuals, have beneficial, rather than negative effects, such as increased growth rates or better reproductive performance (e.g., Schöpper et al. 2012; Dantzer et al. 2013; Crino et al. 2014). From an evolutionary perspective, adjusting the responsiveness to stressful events in response to early-life adversities by programming of the HPA axis could be adaptive if this would lead to phenotypes better able to cope with environmental conditions that are more likely to be experienced later life. This view is the basic concept of the "environmental matching hypothesis" (sometimes also termed as "predictive adaptive response"—Gluckman and Hanson 2007; Gluckman et al. 2007; Horton 2005; Fig. 4.2b). According to this hypothesis, the developing organism responds to environmental signals by a lasting alteration of physiological regulatory circuits, most notably the HPA axis, in order to be better adapted to its current and expected future environment. A heightened HPA response and increased anxiety, for instance, while usually considered maladaptive, can be highly adaptive in an environmental context characterized by adversity and unpredictability. A mismatch between environmental conditions experienced in early development and later life, however, is suggested maladaptive and may increase the risk of earlier mortality (Gluckman et al. 2007, 2010; Horton 2005). In line with this, individuals with a history of childhood adversity exhibited a dampened HPA axis in response to acute stress in adulthood (Elzinga et al. 2008), whereas a mismatch between childhood and adult environments was found to increase the vulnerability to psychopathology (Nederhof

and Schmidt 2012; Fine et al. 2014). In addition, although in humans and primates, an increased risk to develop psychopathology after early-life exposure to traumatic stress has been reported, some studies also found a higher degree of resilience in terms of active coping with stressful conditions experienced in later life (Lyons and Parker 2007; Zozulya et al. 2008). Evidence for the match/mismatch hypothesis also comes from rodent studies. In rodents as in mammals in general, the mother plays a central role in the context of early-life programming because the environmental cues predictive of the future environment are primarily transferred to the offspring via the maternal physiology and behavior. In rats and mice specifically, the amount of licking and grooming represents an important cue. In accordance with this hypothesis, Champagne (2008) and Bagot et al. (2009) showed that adult offspring of mothers providing only a low amount of licking and grooming exhibited poor cognitive performance (low LG mothers) in a low-stress context. But under stressful conditions, cognitive performance of adult offspring of low LG mothers was superior to the performance of adult offspring that had received a high amount of licking and grooming and showed impaired cognitive performance in such a high-stress context (Champagne 2008; Bagot et al. 2009). Developmental programming effects associated with environmental matching cues might be enhanced when similar stressors are experienced across multiple developmental life stages within the same individuals. Some evidence for this comes from a study in the Japanese quail in which birds exposed to both pre- and post-natal stress-related treatments (prenatal corticosterone injection and unpredictable food availability, respectively) were more explorative and risk-taking in a novel (presumably stressful) environment, compared to the birds that were exposed to stress only as embryos or as chicks (Zimmer et al. 2013). One of the main criticisms about the studies conducted so far in support of the existence of predictive adaptive responses is that the vast majority of the work has been carried out in captive animals and humans, and often exposed to artificial or extreme stressors that may hardly represent evolutionary relevant conditions (see Berghänel et al. 2016 for a discussion on this aspect).

Indeed the actual severity of early-life adversity is likely to be an important contributory factor regulating subsequent stress resilience. Suggestions for this comes from research in humans highlighting that a history of some early-adversity can foster subsequent resilience compared to individuals with a high history of adversity but also to people with no history of adversity. For instance, moderately stressful events during childhood had been associated with decreased cardiovascular responses to stressful laboratory tests (Boyce et al. 1995), lower levels of anxiety (Edge et al. 2009), diminished cortisol activity (Elzinga et al. 2008; Gunnar et al. 2009), lower post-traumatic stress symptoms and distress (Seery et al. 2010). Research in mammalian laboratory models supported and extended these findings. For instance, short-term exposure to certain early-life stressors (intermittent social and/or maternal separations, high-demand foraging conditions) in rats and squirrel monkeys has been shown to attenuate anxiety-like behavior and diminish HPA axis reactivity compared to individuals raised under less stressful conditions (Parker and Maestripieri 2011). Individuals with an enhanced efficiency of the negative feedback would be able to bring glucocorticoids faster back to baseline levels upon exposure

to challenging events and, therefore, have reduced probability to suffer from potential harmful effects of chronic glucocorticoid exposure (Taff et al. 2018; Zimmer et al. 2019). Taken together, these findings suggest nonlinear associations, probably U- or J-shaped associations, between early-life stress and later life resilience (Parker and Maestripieri 2011; Russo et al. 2012).

Little is known about the mechanisms that promote the development of stress resilience. As early handling in rodents is known to increase maternal licking and grooming (Liu et al. 1997), it was first hypothesized that the development of stress resilience was predominantly maternally mediated (*maternal mediation hypothesis*—Caldji et al. 2000; Plotsky and Meaney 1993). However, seminal experiments by Parker and colleagues in squirrel monkeys, a model in which brief intermittent maternal separation stress does not lead to changes in maternal behavior, demonstrate that it is stress exposure per se, rather than maternal care, to have a key role (Parker et al. 2006). These studies supported the alternative "*stress-inoculation hypothesis*" (Fig. 4.2c), which is based on the notion that mild-to-moderate stress exposure is necessary for the development of appropriate emotion regulation and subsequent stress resilience (Parker and Maestripieri 2011; Romeo 2015). This concept is related to that of "hormesis," a type of dose–response relationship with low dose inhibition and high dose stimulation of organism performance (see Chap. 2 in this book), which might complement the inoculation model.

In the inoculation model, resilience arises from intermittent exposure to early-life stressors that are not overwhelming, but just challenging enough to transiently activate the HPA axis (Parker et al. 2005, 2006). The mechanisms leading to a resilient phenotype are likely to involve life-long changes in the brain and pituitary gland, which might be associated with increases in glucocorticoid and/or mineralocorticoid receptors (Zimmer and Spencer 2014; Sapolsky 2015; Marasco et al. 2016). Glucocorticoid receptor signalling has a key role in the regulation of HPA axis negative feedback (Cornelius et al. 2018; Dickens et al. 2009). The immunophilin FKBP5, a glucocorticoid receptor cofactor with inhibitory effect on glucocorticoid activity, is associated with individual differences in HPA axis negative feedback efficiency (Touma et al. 2011; Häusl et al. 2021) as well as altered risks of anxiety and post-traumatic stress disorder (Touma et al. 2011; Hariri and Holmes 2015). A recent study performed by Zimmer et al. (2021) in wild house sparrows (*Passer domesticus*) showed that reduced mRNA expression of FKBP5 in the hypothalamus was associated with higher HPA axis flexibility (i.e., within-individual, rapid and reversible change in HPA regulation in response to challenges) and improved stress coping capacities in terms of exploratory disposition, neophobia, and body mass maintenance. Although FKBP5 is sensitive to early-life conditions (review: Zimmer et al. 2020), whether this marker could capture long-term changes in physiological stress resilience and fitness outputs remains to be tested, offering a very exciting question to address in future research.

4.3.2 Telomere Dynamics and Oxidative Stress

There is considerable evidence across a wide range of vertebrate taxa that dynamics in telomere length and oxidative stress are two key cellular mechanisms that affect organism performance (Monaghan et al. 2018; Costantini 2019). Given the profound and long-lasting effects of glucocorticoids on physiological homeostasis and their properties to translate environmental stimuli into molecular responses, some authors suggested that they might be key molecular links between environmental quality and both telomere dynamics and oxidative stress (Costantini et al. 2011; Angelier et al. 2018). However, these hypotheses have been poorly explored so far in the context of early-life phenotypic programming.

In 2013, Marasco et al. (2013) provided experimental evidence for a role of early-life exposure to glucocorticoids in affecting some aspects of adult oxidative status. Marasco et al. (2013) used an experimental setting including four groups: pre- and postnatal untreated birds; prenatal corticosterone-treated and postnatal untreated birds; prenatal untreated and postnatal corticosterone-treated birds; pre- and postnatal corticosterone-treated birds. The manipulation of prenatal stress levels involved the injection of eggs of Japanese quail (*Coturnix japonica*) with 8.5 ng of corticosterone dissolved in peanut oil. The postnatal stress treatment involved the administration to chicks of one mealworm (*Tenebrio molitor*) per day injected with 45 μg (between 5 and 15 days of age) or 90 μg (between 16 and 19 days of age) of corticosterone dissolved in peanut oil. Both pre- and post-natal treatments with corticosterone were chosen in order to increase corticosterone within the age-specific physiological ranges of the study species. The effects of the experiment were then tested on four markers of oxidative status, analyzed in red blood cells collected at 64 days of age and in the brain (cerebellum and midbrain) at 69–73 days of age (Marasco et al. 2013). In red blood cells, there was no effect on the antioxidant enzyme superoxide dismutase nor on the marker of oxidative damage protein carbonyls. The activity of the antioxidant enzyme glutathione peroxidase was higher in all the corticosterone-treated birds than in controls, but there was an additive effect in birds that experienced both the pre- and post-natal treatment. Finally, a marker of nonenzymatic antioxidant capacity was lower in corticosterone-treated birds than in controls. All the markers of oxidative status were not affected in the midbrain; by contrast, in the cerebellum the glutathione peroxidase was marginally higher in the three corticosterone-treated groups and the nonenzymatic antioxidant capacity was lower in the birds that experienced both the pre- and the post-natal treatment than those that experienced only one of the two treatments. Overall, this experimental work suggested that increased exposure to corticosterone in ovo influenced the adult oxidative phenotype, possibly through direct effects on cell metabolism, gene expression, or growth rate. Importantly, the nature of effects depended on the interaction between pre- and post-natal environments, suggesting a certain degree of plasticity in the regulation of oxidative status and providing some support to the environmental matching paradigm, at least for certain aspects of oxidative status.

These interactive effects of early-life challenges on oxidative status were later shown using unpredictable food supply (which generally leads to increases in plasma corticosterone—e.g., Pravosudov et al. 2001; Marasco et al. 2018) in another precocial bird species, the gray partridge (*Perdix perdix*) (Homberger et al. 2013). Birds had higher blood antioxidant capacity when they experienced no stress in both the pre- and post-natal stages of life, and had lower antioxidants when experienced food stress only after hatching. By contrast, the production of free radicals in blood was not influenced by the stress regime, suggesting that trophic stress affected only some aspects of the antioxidant machinery. It is important to highlight that alterations of the HPA axis activity are one effect of unpredictable food supply (e.g., Lynn et al. 2003; Wingfield 2003). Thus, the results from Homberger et al. (2013) strengthen the hypothesis of Marasco et al. (2013) that the adult oxidative status will depend to some degree on the precocial exposure to different amounts of glucocorticoids. However, it appears to give more support to the silver spoon model because antioxidant capacity was preserved only when birds did not experience any stress both in early- and in adult-life.

It is unknown if these long-term effects on oxidative status have any fitness consequences. The strategy of depositing glucocorticoids into the eggs may be adaptive if any physiological costs for the chicks are lower than the benefits. This may be especially true for chickens and quail, as well as for other precocial species. Compared with altricial chicks, precocial chicks leave the nest soon after hatching and rely less on maternal care. Therefore, they have to be programmed to survive almost on their own very soon in life. Glucocorticoids may be important promoters of survival because they enhance fear and vigilance behaviors, so allowing precocial chicks to avoid predators or to stay close to their siblings (Hayward and Wingfield 2004; Janczak et al. 2007). Moreover, chickens and quail are short-lived species; therefore, they might have been programmed to prioritize investment in growth and reproduction at the expense of investment in protection against oxidative stress. Although these are still almost unexplored questions, a few studies suggested that the link between early-life exposure to glucocorticoids and oxidative status might be relevant for later fitness outcomes and for adjusting the phenotype to environmental challenges of the Anthropocene. Zimmer and Spencer (2015) showed that pre-natal experimental exposure to glucocorticoids may be associated with a higher cost of reproduction in terms of oxidative stress in the Japanese quail. Using the brown trout, Birnie-Gauvin et al. (2017) evaluated the short-term (2 weeks) and long-term (4 months over winter) effects of exogenous cortisol manipulations (as well as relevant shams and controls) on the oxidative status of wild juveniles. Cortisol caused an increase of the antioxidant glutathione in red blood cells over a two-week period and appeared to reduce glutathione over winter (Birnie-Gauvin et al. 2017). By contrast, cortisol treatment did not affect the ratio between reduced and oxidized glutathione nor a marker of antioxidant capacity. Importantly, over winter survival in the stream was associated with low levels of glutathione, suggesting that oxidative stress might be a mechanism by which elevated early-life exposure to cortisol causes negative physiological consequences (Birnie-Gauvin et al. 2017). Flores et al. (2019) evaluated the effect of traffic noise (traffic noise

group vs. rural noise group) on baseline levels of corticosterone and stress responses in chicks of the Japanese quail. They observed (i) similar baseline levels of corticosterone in both experimental groups, (ii) a trend towards higher stress response in the traffic noise group, (iii) higher levels in red blood cells of the key intracellular antioxidant glutathione in the traffic noise group, and (iv) a negative effect of stress response on glutathione in the traffic noise treatment.

As compared to research on the link between early-life stress and oxidative status, much less is known for the long-term effects of early-life stress on adult pattern of change in telomere length. This is particularly unfortunate because in the majority of vertebrates studied so far, the highest rates of telomere shortening are observed during early development (Heidinger et al. 2012; Monaghan and Ozanne 2018). Studies in wild birds, including European shags (*Phalacrocorax aristotelis*) and great tits (*Parus major*), demonstrated that experimental exposure to corticosterone during early postnatal development fostered developmental telomere shortening (Herborn et al. 2014; Casagrande et al. 2020). However, a recent study in wild yellow-legged gulls showed that pre-natal corticosterone exposure led to telomere elongation and upregulated telomerase activity in the juveniles (Noguera et al. 2020). Many factors could explain differences among studies, such as the developmental timing in which stress exposure was experienced and the time in which telomere measurements were made. The severity of the stress exposure is likely to be especially important. An experimental study in the domestic chicken (*Gallus domesticus*) performed by Haussmann and collaborators (2012) showed that only very high prenatal glucocorticoid exposure increased developmental telomere loss, while a low prenatal corticosterone exposure had no effect (Haussmann et al. 2012). Importantly, in the latter study, only the high prenatal corticosterone exposed birds showed clear signs of HPA axis hyper-responsiveness compared to the other two treatment groups (Haussmann et al. 2012). It is thus possible that modest or brief activations of the HPA axis during development may trigger telomere repair mechanisms including up-regulated telomerase activity, while more severe or chronic stress exposure downregulate telomerase activity. Plausibility for such nonlinear inoculation-like effects comes from studies in rodents showing that a brief exposure to certain environmental stressors can rapidly increase telomerase activity (Beery et al. 2012; Epel and Lithgow 2014). We need more ecologically relevant experimental designs to further explore the links between early-life exposure to different amounts of glucocorticoids, telomeres, and oxidative status. We also suggest exploring if glucocorticoid-induced effects are associated with changes in mitochondrial metabolism (Casagrande et al. 2020). This is particularly intriguing because, on one side, mitochondria are one main source of prooxidant generation in organisms, and, on the other side, they produce the molecule ATP, which provides energy for growth and development.

4.3.3 Epigenetic Mechanisms Regulated by Glucocorticoids

Rapidly growing evidence suggests that the underlying mechanisms through which early-life conditions are biologically embedded and may exert lifelong effects, involve epigenetic processes (see Chap. 1 for a comprehensive review about the understandings of the term "epigenetics" and related molecular mechanisms). This is because the epigenome regulates gene expression in a cell and tissue-specific manner. Thus, without modifying the genome itself, the epigenetic machinery determines the actual phenotypic outcome by regulating what is transcribed from the genome. Second, the epigenome is responsive to environmental influences, providing the biological basis for the interplay between environmental cues and the genome. Epigenetic remodelling caused by early-life experiences, therefore, serves as an ideal mechanism for developmental plasticity. Third, epigenetic modifications are stable and steadily transferred from one cell generation to the next. In this way, the epigenome facilitates long-lasting modifications of gene expression patterns caused by early-life environmental signals and, therefore, from an evolutionary perspective, provides a means to "fine-tune" the phenotype to forecast future conditions. Indeed, numerous studies have shown that early-life experiences can induce epigenetic modifications that cause persistent changes in gene expression patterns and thus exert long-term effects on phenotypic outcomes. Although identifying epigenetic modifications associated with any phenotypic outcome alone does not imply causality, numerous studies have provided strong evidence for a functional relationship through the analyses of mRNA expression (e.g., McGowan et al. 2009; Labonte et al. 2012).

Genes regulating the HPA axis are prime candidates for investigating how early-life stress can be biologically embedded by epigenetic modifications. Accordingly, one of the most renowned examples of epigenetic programming examined the effects of maternal care on epigenetic remodeling of genes involved in HPA axis function. This series of studies by Weaver, Meaney, Szyf, and colleagues demonstrated in rats, how natural differences in maternal behavior can lead to epigenetic programming inducing life-long changes in offspring behavior and physiology (Weaver et al. 2004; Meaney and Szyf 2005). The authors demonstrated that high levels of maternal licking and grooming during the first week of life resulted in higher mRNA expression of the glucocorticoid receptor gene in the offspring hippocampus caused by lower DNA methylation and higher histone acetylation of the glucocorticoid receptor promoter exon 17. The methylation difference was located at the binding site of the transcription factor nerve growth factor inducible A (NGFI-A), where in offspring of low licking mothers, methylation levels are high, impeding transcription factor binding and thus glucocorticoid receptor gene expression. The alteration of DNA methylation in response to maternal licking and grooming remained stable into adulthood, leading to life-long changes in HPA axis function of the offspring. In offspring of high licking mothers, higher hippocampal glucocorticoid receptor expression increased negative feedback sensitivity of the HPA axis, which ultimately resulted in lower endocrine and behavioral responses to stress and

reduced fearfulness in the presence of a stressor such as a novel environment. Cross-fostering experiments (offspring of high LG mothers were fostered by low LG mothers and vice versa) demonstrated that indeed the differences in maternal care caused the epigenetic modifications and thus determined the offspring phenotype. This research provided strong evidence for a causality between early-life epigenetic programming and phenotypic outcome in adulthood as the epigenetic alterations induced by maternal behavior and its effects on gene expression and stress response in the offspring could be reversed in adulthood by central infusion of either methionine, affecting DNA methylation, or a histone deacetylase inhibitor, affecting histone acetylation (Weaver et al. 2004, 2006). In addition, these findings were also extended to humans. McGowan et al. (2009), for instance, showed that methylation of the human homologue of the hippocampal glucocorticoid receptor promotor region was increased and mRNA expression reduced in suicide victims that had a history of childhood abuse.

Genes, however, do not act independently. Even though the candidate gene approach is valuable as it has first shed light into the epigenetic mechanisms underlying programming effects of early-life experiences, the impact of early-life experiences is broader, involving numerous genes in a tissue-specific manner (e.g., Marasco et al. 2016). The advent of epigenome-wide association studies and transcriptomics now facilitates a more realistic analysis of epigenetic modifications induced by early-life experiences on the basis of the whole genome rather than a limited set of candidate genes. Interestingly, a recent study by Taff et al. (2019) on free-living female tree swallows (*Tachycineta bicolor*) showed associations between differentially methylated regions across the genome with stress resilience to handling (i.e., the ability to terminate the glucocorticoid stress response through negative feedback). The latter study thus indicates that global methylation patterns may predict stress coping abilities and possibly fitness consequences in natural settings, and might act as a useful biomarker of stress resilience. Taff et al. (2019) hypothesized that the differentially methylated regions identified in their study in relation to stress physiology might be due to early-life programming effects. At least to a certain extent, support for this explanation comes from a study showing that zebra finches raised in broods of different sizes (thus likely experiencing different early-life stress exposure levels due to changes in food availability and sibling competition) showed consistent hypo- or hypermethylation across the genome (Sheldon et al. 2018). Future experimental studies are, however, needed in order to determine whether large-scale regulation of methylation patterns in early-life is a causal driver of subsequent stress reactivity and coping abilities.

4.4 Conclusions and Future Directions

A large body of evidence from epidemiological and animal experiments clearly shows that exposure to early-life stress can have a remarkable influence on adult lifestyle and health outcomes. Detailed studies carried out in model organisms

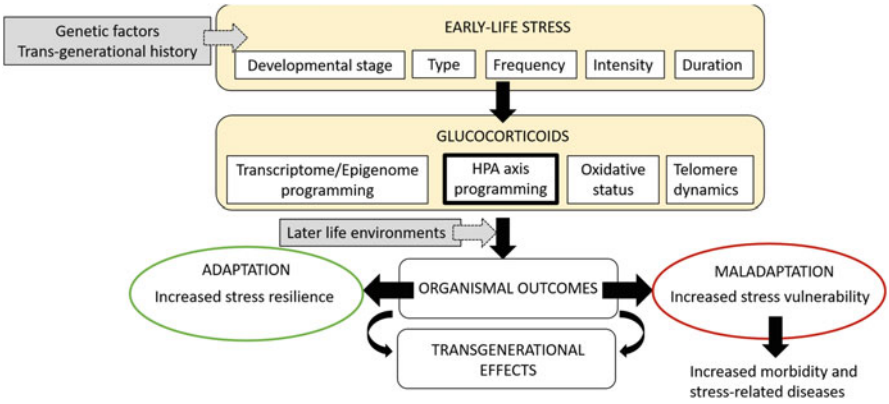

Fig. 4.3 Conceptual model of early-life stress programming. Exposure to stress during pre- and post-natal stages of development leads to increased exposure to glucocorticoid hormones. Elevated developmental glucocorticoids can lead to long-lasting changes in the Hypothalamic–Pituitary–Adrenal (or Interrenal) axis (HPA axis) activity (likely to play a central role in the shaping of phenotypic trajectories) and other molecular mechanisms underlying aging and life-history evolution including transcriptome and epigenenome regulation, oxidative status, and telomere dynamics. The phenotypic effects of early-life stress depend on an organism's genetic background and on its trans-generational history, as well as on the developmental timing in which stress exposure occurs and specific features of the challenge/s (type, frequency, intensity, and duration). Interactive effects among these factors would determine subsequent resilience or vulnerability to later life challenges, and thus explain inter-individual variation in organismal and fitness outcomes of stressed-exposed phenotypes

demonstrated that the HPA axis is likely to be a key physiological system underlying the programming effects of early-life adversity (Fig. 4.3). However, there has been increasing recognition that such effects operate at multiple biological scales and encompass more pervasive cellular and molecular changes. Current evidence suggests that measurements of telomere dynamics, oxidative status, and transcriptome/epigenetic networks are relevant mechanisms and markers to trace the long-lasting effects of early-life experience on performance and fitness-related proxies. However, whether these markers can be considered as main modulatory signals orchestrating some of the programming effects of early-life stress remains to be determined. Carefully designed experiments, for instance, manipulating an organism's oxidative status during growth (e.g., by increasing generation of pro-oxidants or decreasing antioxidants along a low-high stress severity gradient) is now within reach in most ecological settings (Koch and Hill 2017) and would be very useful in this context. In addition, the ongoing advances in "omics" approaches constitute an exciting opportunity to characterize, and potentially manipulate, conserved transcriptome pathways and epigenetic mechanisms influenced by a particular level of stress exposure and to identify target brain structures in which such changes effectively operate and lead to long-term differences in stress susceptibility versus resilience.

The studies reviewed throughout this chapter clearly highlight that early-life stress does not necessarily lead to undesired adverse outcomes in adulthood.

While extreme and/or prolonged stressors do often impair brain development, increase susceptibility to later life morbidities, and lower survival prospect of an organism, newer research suggest that milder forms of stress exposure, such as brief maternal separation or moderate physiological elevation of developmental glucocorticoids, can instead increase the range of tolerable stress for the organism and potentially ameliorate later life performance and delay aging processes. Yet, we have limited experimental data that explicitly manipulated the severity of stress exposure of differing types of early-life challenges and examined subsequent changes in relevant molecular/physiological pathways and fitness outcomes. Plus, stressor type and severity are likely to be interconnected with other biological features which need to be carefully considered when planning experiments, especially developmental timing of stress exposure, species-specific developmental strategies, and the later life environmental conditions experienced throughout an organism's lifecycle (Fig. 4.3). Another aspect often overlooked in experimental planning is that a considerable inter-individual variability in the ontogeny of the stress response is merely attributable to genetic predisposition factors or to the trans-generational history of the study population (McIlwrick et al. 2016; McCormick et al. 2017—Fig. 4.3). As a consequence, similar or even the same early-life challenge could have major negative consequences for one individual or population, and have negligible or even positive effects in another. Understanding the relative contribution of all these factors on the biological embedding of early-life stress is a critical step forward in order to better define how just the right type and magnitude of stress inoculation can promote resilience processes and potentially shape phenotypes with better suited coping mechanisms to maximize fitness outputs.

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Chapter 5
Environmental Conditions in Early Life, Host Defenses, and Disease in Late Life

Gabriele Sorci and Bruno Faivre

Abstract Immunity is an essential function for host homeostasis through its action on the control of pathogenic organisms and malignant cells. Immune defenses also require a finely-tuned regulation to avoid collateral damage due to overreacting responses and self-attack. Because of its central role for organismal fitness, the expression of immune traits has been proposed to mediate the negative covariation (trade-offs) between life history traits. These trade-offs can involve traits that are expressed at the same age or at different ages (early vs. late life traits). The magnitude of the trade-offs (as well as the sign of the covariation between early and late life traits) has a strong environmental modulation. Early environmental conditions experienced during key stages of the development of the organism have the potential to induce long-term carry-over effects on the whole suite of life history traits, defense strategies against pathogens and longevity, through immune-mediated mechanisms. Here, we provide an overview of the possible environmental features experienced in early life that can affect defense strategies and disease at late age. Our review stresses the complexity of the synergetic effects linking environmental traits, the activation and education of the immune system, defense strategies, the expression of age-dependent life history traits, susceptibilities to infection, and immunopathology. At the current stage of knowledge, context-dependent effects seem ubiquitous, preventing to have general and consistent predictions on how the *n*-dimensional environment will affect pattern of disease at late age, through early-immune modulation. Perhaps due to our "simpler" environment and a better knowledge of the functioning of the immune system and its regulation, studies on humans have more consistently showed that early exposure to some environmental traits (e.g., low diversity of environmental microorganisms) is indeed associated with dysregulated immune functions and increased susceptibility to infection and inflammatory diseases at late age.

G. Sorci (✉) · B. Faivre
Biogéosciences, CNRS UMR 6282, Université de Bourgogne Franche-Comté, Dijon, France
e-mail: gabriele.sorci@u-bourgogne.fr; bruno.faivre@u-bourgogne.fr

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5.1 Introduction

Environmental conditions experienced in early life, which include the prenatal environment, have profound consequences for the development of the phenotype and organismal fitness (Lindström 1999; Monaghan 2008). In humans, early effects of environmental conditions on health and disease have been recognized since a few decades and led to the "developmental origin of health and disease" (DOHaD) hypothesis (McMillen and Robinson 2005). The DOHaD hypothesis posits that early exposure to nutritional stress (including in utero exposure) sets a series of epigenetic alterations that subsequently affect the risk of disease during adulthood. In agreement with the hypothesis, several epidemiological studies on human cohorts have reported associations between poor fetal and early postnatal nutrition and the risk of type 2 diabetes and cardiovascular diseases (Hales et al. 1991; Barker et al. 1993; Hales and Barker 2013). For instance, children born from women who experienced the Dutch famine during "hunger winter" of the World War II, when becoming adults, were found to have increased risk of suffering from metabolic disorders (Ravelli et al. 1976).

In nature, free-living species are exposed to a multitude of environmental stressors that, in addition to the amount of trophic resources, can also include high burden of pathogens and parasites, high density of competitors or predators, or unsuitable thermal conditions. These and many other environmental factors can shape the whole suite of life history traits that characterize the individual pace of life (early vs. late age at maturity, high vs. low investment into early reproduction, high vs. low investment into somatic maintenance), through direct effects on the developmental program. Reduced food availability during prenatal and early postnatal life can have instantaneous effects by stunting growth rate and delayed effects depending on the amount of compensatory growth that might follow the initial food restriction (Ozanne and Hales 2004; Criscuolo et al. 2008; Lee et al. 2016). Whatever the underlying mechanisms, considering the long-term fitness consequences of early environmental conditions is primordial for our understanding of the evolution of life history traits and aging (Cooper and Kruuk 2018).

Developmental plasticity refers to the capacity of the organism to respond to changes in the environmental conditions encountered during critical stages of development (Barker 2004). However, this capacity is also constrained by canalization, which limits the range of the possible phenotypic values (Flatt 2005). With this respect, the immune system stands out as one of the most plastic physiological functions whose maturation and "education" tightly depend on input from the environment (Rook 2013; Martin et al. 2021). As any body function, the immune system requires metabolic resources, both at its steady state and especially so when the immune response is induced following an infection (Straub et al. 2010; Bajgar et al. 2015). Therefore, any environmental factor that shape the amount of energy organisms can afford to acquire is likely to determine how much of this energy can be allocated to the immune function. This is essentially similar to the general mechanism underlying the principle of resource allocation (Stearns 1992); assuming

that the pool of available energy is limited and that several functions compete for this restricted amount of resources, poor environmental conditions experienced during early life can set a limit to the development of immune organs, cells, signaling molecules, etc. Environmentally (resource) driven immune impairment can of course alter the organismal capacity to face an infection and as such affect infection-induced mortality and/or reproductive success (McKay et al. 2016). For instance, weaning Wistar rats raised under a protein-reduced diet have lower eosinophil counts, reduced numbers of mast and goblet cells, and lower amount of specific antibodies against the nematode *Trichinella spiralis*; and nematodes infecting protein-deprived rats persist for longer and have higher fecundities (Vila et al. 2018). Therefore, when organisms live in poor environments, reduced immune capacity to fight off pathogens and parasites can result in compromised fitness.

However, considering that an enhanced immune response, due to abundant resources, is always associated to improved host fitness might reveal misleading. Indeed, although the main function of the immune system is to combat infection, this goal has to be achieved while avoiding attacking host cells and organs (Sell 2001; Bergstrom and Antia 2006; Sorci et al. 2013). Actually, fitness costs associated with immune dysfunctioning can be due to both impaired and overreacting immune responses (Sorci et al. 2017). Therefore, food-supplementation can also induce immune-associated costs, if the immune response is not properly regulated or the associated damage is not repaired (Stahlschmidt et al. 2015). For instance, food-supplemented domestic canaries (*Serinus canaria*) are better able to limit pathogen proliferation when infected with the haemosporidian *Plasmodium relictum*, but they suffer from a reduction in red blood cell number, possibly due to an exacerbated immune response (Cornet et al. 2014). In addition to this, when hosts are able to gather large amount of resources, they might also provide good environmental conditions to parasites. Infection dynamics and parasite virulence may vary depending on whether the immune system and the infecting parasite rely on different types of resources or share the same resources (Cressler et al. 2014; Pike et al. 2019). Actually, the finding that host nutritional status has different effects on host defense and parasite burden in different host-parasite systems is a relatively common observation (Cressler et al. 2014). For instance, food-restricted fruit flies (*Drosophila melanogaster*) have poorer survival prospects compared to ad libitum fed flies when infected with *Listeria monocytogenes*, a better survival when infected by *Salmonella typhimurium*, and similar survival when infected by *Enterococcus faecalis* (Ayres and Schneider 2009) (Fig. 5.1). The effect of a variable amount of resources can actually involve both a modulation of resistance and tolerance to the infection (Budischak and Cressler 2018). Therefore, understanding how the host nutritional status affects its long-term fitness in the face of an infection requires disentangling the complex network of synergistic effects between immune protection, immunopathology, and parasite fitness. This illustrates that environmentally-driven control of the immune response is not merely a matter of quantity (Ramirez-Orozco et al. 2018), and that the regulation of the immune function, as well as the effect on the exploitation strategies implemented by specific pathogens are key for host homeostasis and fitness (Fig. 5.2).

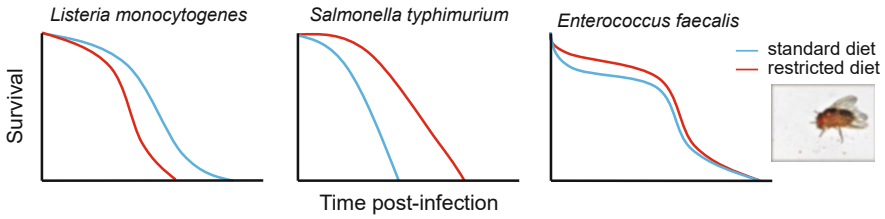

Fig. 5.1 Fruit flies raised under a standard diet or a 50% reduced diet show different survival prospects upon infection with different bacterial pathogens. Food restricted flies (red curves) have poorer survival when infected with *Listeria monocytogenes*, better survival when infected with *Salmonella typhimurium* and similar survival when infected with *Enterococcus faecalis* compared to flies fed a standard diet (blue curves). Survival curves schematically redrawn from Ayres and Schneider (2009) for illustrative purposes. *Drosophila melanogaster* (Image credit: Rolf Dietrich Brecher, https://upload.wikimedia.org/wikipedia/commons/0/03/Drosophila_melanogaster_%E2%99%80_%2838978426500%29.jpg, CC-BY-2.0, https://creativecommons.org/licenses/by/2.0/)

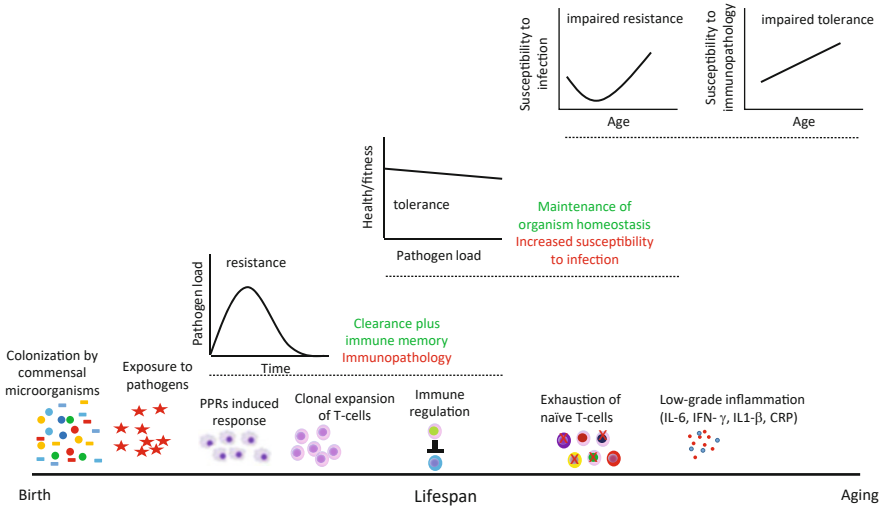

Fig. 5.2 Schematic representation of key immune steps during a vertebrate host lifespan. At birth, the host is colonized by commensal and mutualistic microorganisms with auxiliary functions. During the ontogeny, the host will also encounter pathogens potentially representing a threat for health and homeostasis. Upon recognition by PRRs, the host mounts an immune response involving, among others, the expansion of T- and B-cells. This response is instrumental to keep pathogen proliferation under control and clear the infection. Benefits of the immune response involve host resistance, costs occur if the immune response induces collateral damage. To minimize this collateral damage, several immune pathways ensure the regulation of the immune response. A finely-tuned immune regulation can confer a benefit in terms of maintenance of host homeostasis in the face of the infection (tolerance), but can also incur a cost in terms of increased susceptibility to infection. Resistance and tolerance might therefore trade against each other. As the host ages, naïve T cells get exhausted and the involution of the thymus prevents their replacement. In addition to this, age induces a shift towards low-grade inflammatory status characterized by an overproduction of pro-inflammatory cytokines and markers. The exhaustion of naïve T cells and a pro-inflammatory status result in increased susceptibility to infectious diseases and immunopathology at old age

Interestingly, although endogenous mechanisms of immune tolerance allow the host to regulate immunity, environmental factors play a fundamental role in instructing the immune system to (i) discriminate between harmless antigens and dangerous pathogens, and (ii) down-regulate potentially harmful inflammatory responses. Exposure to environmental microbial diversity, which constitutes the community of commensal organisms that colonize epithelia, provides such "educational" function (Schroeder and Backhed 2016; Brown and Clarke 2017). Therefore, variation in environmental exposure to commensal microorganisms during early life can have long-lasting effects on the host capacity to deal with infection and avoid disease, as shown in humans and model systems (O'Sullivan et al. 2013; Arrieta et al. 2014; Gensollen et al. 2016; Kemp et al. 2021). This adds an additional layer of complexity in the relationship between early environmental conditions and the functioning of the immune system.

Immune tolerance is a very important function, because lack of immune tolerance can produce devastating effects in terms of immunopathology and autoimmune damage, both in the presence or in the absence of an infection (Kim et al. 2007; Shin et al. 2016). However, the immune system also plays a role in another concept that has emerged during the last decade and that refers to the organismal capacity to tolerate the infection. Tolerance to infection is the strategy that minimizes the fitness cost of the infection, independently of the actual pathogen load (Ayres and Schneider 2012). Although immune tolerance and tolerance to the infection are not synonymous terms, in many instances, a regulated immune response improves tolerance to the infection (Allard et al. 2018). For instance, the expression of the transcription factor Gata3, which mediates the Th2 immune response, has been shown to increase tolerance to helminth parasites in male field voles (*Microtus agrestis*) (Jackson et al. 2014). As such, if the environmentally-driven education of the immune system improves immune tolerance, it can also allow hosts to better facing the cost inflicted by an infection, when such a cost mostly arises by exacerbated inflammation (Graham et al. 2005).

Understanding the fitness consequences of environmental modulation (sensu *lato*) of the immune response also requires taking into account the age-associated changes that occur during the individual lifespan. Immunity and infection (both risk and cost) are known to change from birth to aging, usually in a non-linear way. Moreover, while environmental factors shaping immune functioning can affect the infectious risk at any given age, they can also produce delayed effects that can possibly appear from days to years after the exposure to the particular environmental condition, depending on the life cycle of the organism (Guivier et al. 2018). Such delayed effects have the potential to decouple the effect of the current environment on the emergence of immune-associated disorders, susceptibility to infection, and fitness costs. Therefore, past history of infection can have positive or negative long-term consequences on host fitness. On the one hand, previous exposure can shape the host capacity to resist and/or tolerate infection with other pathogens, depending on the amount of cross-reactivity and immune tolerance induced by pathogen encounter during early life. On the other hand, activation of the inflammatory response during early life might also increase mortality at late age, suggesting that exposure to

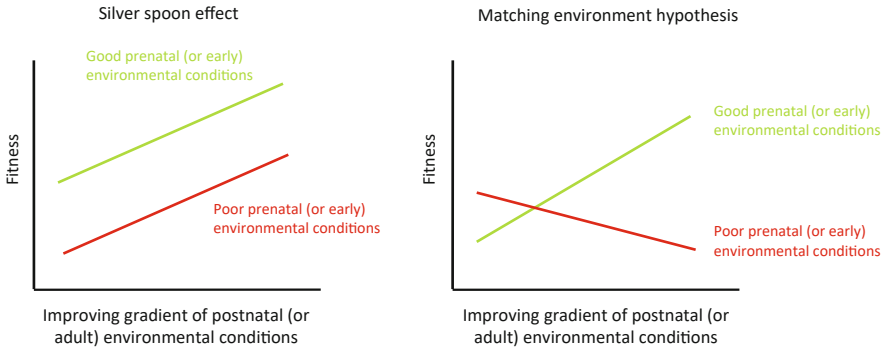

Fig. 5.3 Environmental conditions experienced during early and late life may have additive or interactive fitness effects. Additive effects of early and late environments imply that individuals born in good environments maintain a selective advantage whatever the quality of the environment experienced in late life, the so-called silver spoon effect. If early and late environments have interactive effects, organismal fitness is maximized when there is a match between the two, whatever their quality. According to the matching environment hypothesis, individuals born in poor environments might achieve higher fitness than individuals born in good environments, provided that they encounter the same conditions at adulthood. This might work if early poor conditions preadapt individuals to the conditions encountered later on [but see Wells (2007) for a critical discussion of the matching environment hypothesis]. For the sake of simplicity, only two early environments are represented. Adapted from Pigeon et al. (2019)

inflammatory stimuli when young might advance the onset of actuarial senescence and accelerate its rate (Finch and Crimmins 2004).

Temporal variation of environmental conditions at the scale of the individual lifespan is another key feature that has been suggested to play a role on the adaptive nature of carry-over effects of early environmental conditions. If we admit that the environment varies at the spatial scale, and therefore some individuals will experience better perinatal conditions than others, would this initial difference persist independently of the suite of environmental conditions that individuals are going to encounter during their subsequent life? To this respect, at least two scenarios can be put forward (Fig. 5.3). Favorable initial environmental conditions might give a permanent benefit whatever the environment encountered in future life (i.e., the silver spoon effect) (Grafen 1988). Alternatively, early environmental conditions may predispose the organism to express phenotypic traits conferring maximum fitness under these very specific conditions. Therefore, fitness might vary depending on whether early and late environmental conditions do or do not match (the environmental matching hypothesis) (Gluckman et al. 2005). Assessing if early and late environments match requires considering a multidimensional space that can be described by an n-variable vector. Each entry in the vector refers to one particular environmental trait that can vary over time independently, or in association with the other environmental descriptors. For instance, from an individual perspective, environmental conditions can improve over time because more trophic resources are available, but over the same time, the abundance of parasites and

pathogens can also increase. Based on the criterion used to describe environmental quality, we might therefore draw different conclusions. The relative importance of the silver spoon effect and the environmental matching hypothesis likely depend on how we define environmental variation. For instance, early exposure to some antigenic stimulation predisposes the immune system to rapidly respond if the same epitopes are encountered subsequently during life (a form of matching environment). Therefore, if the infectious environment is stable over time, immune memory confers a selective benefit. On the contrary, if new pathogens emerge and the host has no past experience, immune memory has no benefit.

Despite the complexity of the interactions and synergistic effects that shape how the immune response changes during the individual lifespan, the immune system is an excellent candidate that has to be taken into account if we wish to understand the role played by early environmental conditions as drivers of long-term health and disease risk. The concern about the impact that the unprecedented environmental changes due to human activities might have on biodiversity and human well-being should therefore also focus on any potential effect of such environmental changes on immune-driven diseases. The aim of this chapter is to review how environmental conditions experienced during early life (including parental effects) shape the development of the immune system and how this affects defense strategies during the entire lifespan, including susceptibility to infectious diseases, and inflammatory disorders (Fig. 5.4). As mentioned above, both short- and long-term effects of immune defenses are likely to arise from complex interactions between protection towards infectious diseases (resistance), tolerance to them, and avoidance of immune-associated damage. In the light of the current anthropogenic environmental changes, it seems primordial to identify the environmental features likely to have an impact on immune traits if these modulate the risk of infectious diseases. Before directly addressing the core question of the environmental drivers of immune development and the associated short- and long-term benefits and costs, we will briefly introduce the main features of the immune system, what we know about the link between age and susceptibility to infectious diseases, and how the investment into immune defenses affects host defense strategies (resistance and tolerance) across ages. Although our approach has an evolutionary ecology root, we acknowledge that the study of the immune response in non-model, wild species is still in its infancy. We therefore combined evidence coming from natural systems with those gathered using laboratory or domestic species and humans.

5.2 The Immune System Over the Lifespan

There is little doubt that the immune system represents one of the most vital functions. Given the pervasive threat of pathogens and parasites, hosts with impaired immune defenses pay tremendous fitness costs, essentially in terms of reduced survival prospect. Even seemingly harmless commensal microorganisms might represent a danger for immunocompromised hosts (Ledergerber et al. 1999), because

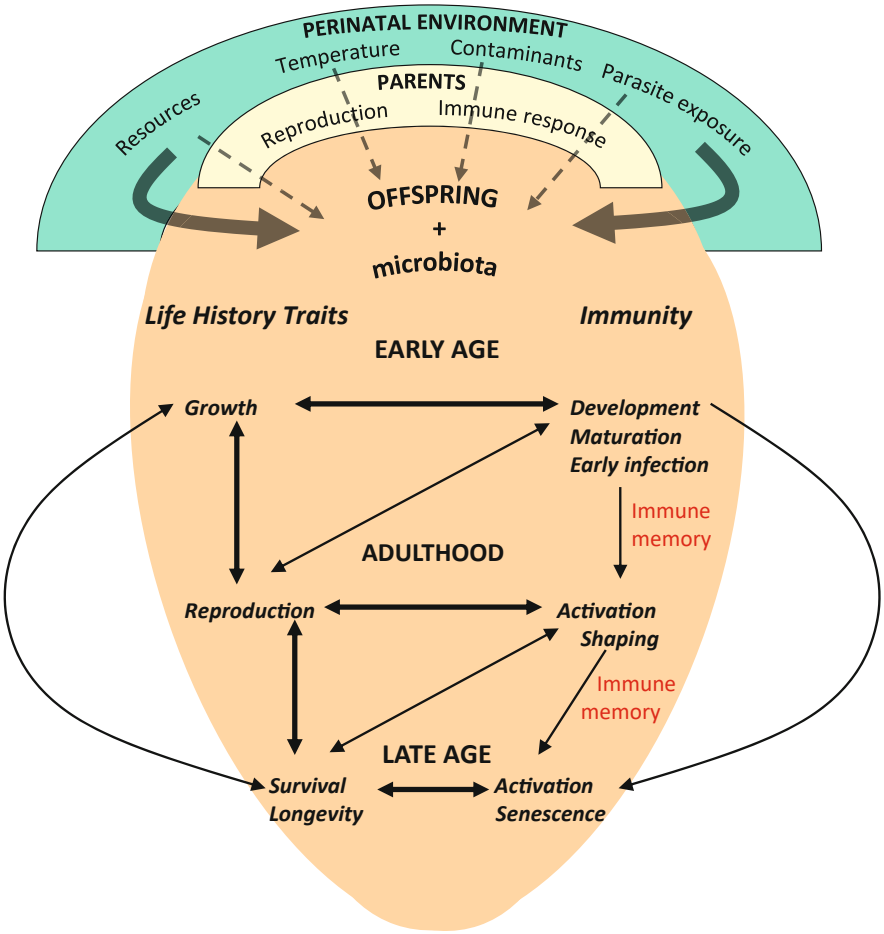

Fig. 5.4 Schematic representation of the complex interactions between early environmental conditions and age-dependent expression of key life history and immune traits. Several perinatal environmental features (that also include the environment experienced by the parents and how this affects parental investment into reproduction and immunity) have the potential to shape the phenotype of the offspring and the microbiota they harbor (a sort of extended phenotype), with instantaneous (early age) and delayed (adulthood and late age) effects. Unidirectional arrows indicate causality links; bidirectional arrows indicate potential trade-offs

the permanent dialog between the immune system and the myriad of commensal species that colonize the host is essential to avoid their proliferation and/or the colonization of vital organs. Keeping track of invading microorganisms is not the only role of the immune system, since its patrolling function also serves other manifold tasks, including the suppression of malignant cells (Schreiber et al. 2011).

A detailed description of the immune system is obviously well beyond the scope of this chapter; nevertheless, it might be useful for the understanding of the

following sections to remind some basic notions of how the immune system works and what are its main features. The key feature of the immune system is to recognize and attack structures that are considered as a danger for the homeostasis of the organism. Although the immune system has the capacity to discriminate between the self and non-self, which allows the immune response to target potentially harmful invaders, this notion was extended to include the capacity to recognize alarm signals, even when the danger comes from cells and tissues of the host (Matzinger 2002). Both models, the self/non-self and the danger model, are based on essentially the same rationale. Pathogens express conserved structures (pathogen-associated molecular patterns, PAMPs) that are recognized by pattern recognition receptors (PRRs) expressed by immune cells (e.g., Toll-like receptors). Similarly, injured, stressed, necrotic cells produce alarm signals (danger-associated molecular patterns, DAMPs) that are also recognized by PRRs and trigger the immune response.

Triggering the immune response therefore always starts when the organism deviates from homeostasis because of internal (danger) or external (infection) reasons. This requires first recognizing an intruder/danger, then producing a suitable set of effectors that possibly clear the infection or eliminate the danger, and finally recover the homeostasis. These three stages and the transitions between them are orchestrated by numerous signaling molecules that recruit, activate, regulate, shut-down immune cells. Therefore, although it might still be useful to distinguish between innate and adaptive immunity, it is more and more clear that these different arms of the immune system are tightly interconnected and can only work in concert (Palm and Medzhitov 2009; Iwasaki and Medzhitov 2015).

The process of resolution of the immune response is a particularly important one because it ensures that immune functions go back to their steady state, once the "danger" sensu *lato* is over. Failure to mount an appropriate immune response because of the inability to recognize the danger or the inability to produce the right effectors can incur costs due to pathogen proliferation; failure to resolve the response and return to a steady state can produce immune damage (Channappanavar and Perlman 2017).

How the immune system develops through the ontogeny has attracted considerable attention from immunologists (Marchant and Kollmann 2015; Georgountzou and Papadopoulos 2017), and also from evolutionary ecologists interested in how environmental conditions affect the outcome of host–parasite interactions (e.g. Adamo et al. 2016). Again, we will not cover all the aspects describing how the immune system matures (from newborns to young adults) and then declines in senescing individuals. However, it seems important to recall that each developmental stage is characterized by specific immune steps that confer age-specific susceptibility/protection patterns (to infection and immune diseases) to the host. During the early stages of the organismal ontogeny, the immune system goes through important steps that allow generating the diversity of clonal lineages of immune cells through positive and negative selection occurring in the thymus (Zerrahn et al. 1997). This establishes the receptor diversity of naïve T cells (TCRs) that allow binding foreign antigenic epitopes, while deleting clones binding to the self. Interestingly, the thymus is an immune organ with a striking pattern of age-dependent involution.

Thymic involution is a conserved phenomenon across vertebrates. The evolution of thymic involution might appear puzzling because age-associated shrinking of the thymus reduces the output of new lineages of naïve T cells. Since the number of naïve clones of T cells declines as the exposure to a diversity of antigenic epitopes increases with age, the depletion of naïve T cells is considered to be one of the major causes of impaired immunity and associated diseases in the elderly (Albright and Albright 2003; Palmer et al. 2018). A possible solution to this paradox refers to the idea that organisms might prioritize different functions during different developmental stages as to maximize fitness. Once a certain amount of TCR diversity has built up, it might be worth to re-allocate limiting resources from the generation of additional T-cell receptors to other functions (e.g., reproduction) (Metcalf et al. 2020).

Although it was thought that newborns and young infants have an "immature" immune system, current evidence suggests that they rather express different immune responses compared to adults and elderly (Debock and Flamand 2014). For instance, they appear to have a less effective immune memory and a highly regulated innate response (MacGillivray and Kollmann 2014). Both findings can be tentatively linked to the environmental conditions faced by newborns and young individuals since immune memory builds up following environmental exposure to microbial antigens, and a regulated innate immunity allows the colonization of commensals bacteria without the induction of harmful inflammation.

As many physiological functions, properties of the immune system show non-linear changes with age. In particular, there is accumulating evidence showing that above a certain age, several immune traits exhibit a series of functional changes that have been collectively called immunosenescence (Nikolich-Zugich 2018). Although immunosenescence includes a large diversity of age-associated modifications in the immune response, the most prominent ones are probably due to the exhaustion of naïve T cells and a skewed immune profile towards a low-grade pro-inflammatory status (Nikolich-Zugich 2018). Such chronic inflammation of the elderly (inflammaging) is actually pointed as a one of the etiologies of age-associated degenerative diseases (Franceschi and Campisi 2014).

Changes in immune functioning from early to late age are mirrored by a similar age-associated susceptibility to infectious diseases (Miller and Gay 1997). In humans, incidence and severity of several infectious diseases across ages have a U- or J-shaped function, with young and old individuals being the most susceptible to the disease and middle-aged adults suffering less, both in terms of incidence and morbidity (Glynn and Moss 2020). However, in other systems, susceptibility to disease has been shown to decrease with age. For instance, daphnia (*Daphnia magna*) infected with the bacterium *Pasteuria ramosa* become less susceptible to the infection as they age (Izhar and Ben-Ami 2015).

While the correspondence between the age-associated pattern of variation between immune functioning and susceptibility of infectious diseases is suggestive of the importance of immune defenses in terms of protection towards pathogens and parasites, it should be made clear that such a macroscopic observation hides more subtle phenomena. For instance, morbidity and mortality due to infectious diseases

can be engendered by fundamentally different processes, such as pathogen proliferation and the associated damage, and/or damage associated with a poorly regulated immune response. Overreacting inflammatory responses such as cytokine storms are actually responsible for high fatality rate in several infections, as for instance shown during the SARS-CoV-2 pandemic (Mangalmurti and Hunter 2020). Age-associated morbidity and mortality might therefore reflect substantially different defense strategies such as resistance and tolerance.

5.3 Strategies of Defense

Although immunity is a central component of the defense towards infection, hosts can implement several strategies that do not necessarily rely on the immune system. Actually, the first line of defense is simply avoiding to be infected and this can be achieved through behavioral responses to a series of environmental stimuli. Humans have evolved an aversion towards rotten food and other potential sources of food-borne infection (Curtis et al. 2004), and although disgust has a cultural component in human societies, animals do also avoid food items that are perceived as risky (de Brooke 2019). Avoidance of infected conspecifics is also a widespread defense strategy that is not restricted to humans or non-human primates (Townsend et al. 2020). Obviously, avoidance cannot provide a full protection against infection for several reasons. For instance, many pathogens and parasites do not alter the behavior or the physiology of their hosts in such a way that one can reliably assess the infectious status of conspecifics, and when reliable cues are not available, the costs associated with avoidance (reduced mating opportunity, social interactions, etc.) might easily outweigh the benefits.

When we cannot avoid being infected, the immune system comes into play. The immune response that is triggered by an infectious insult aims at limiting the proliferation of the pathogen or killing/expelling the parasite, hopefully resulting in the clearance of the infection. The host capacity to keep parasite proliferation under control and clear the infection is referred to as resistance. Therefore, according to this definition, while resistance indicates how good the host is to control pathogen proliferation, it does not tell us whether resistant hosts have a better fitness that susceptible ones. That resistance improves fitness is nevertheless implicitly assumed in many studies, based on the observation that host fitness generally declines as long as pathogen/parasite burden increases (e.g., Mackinnon and Read 2004). Assessing the precise relationship that exists between parasite burden and fitness (or health) allows going a step further. Indeed, on the one hand, individuals that differ in their capacity to control the infection (i.e., have different resistance) might nevertheless have similar survival prospects and reproductive output (especially when the infection involves pathogens with low virulence). On the other hand, individuals with similar resistance (carrying similar parasite burden) might have substantially different health status (fitness). Individuals that have the capacity to limit the fitness (health) cost associated with the infection are more tolerant (can carry high parasite

Table 5.1 Defense strategies and the associated costs and benefits over the lifespan

Defense strategy	Mechanisms	Benefits	Costs	Age-dependent effects
Avoidance	Cognitive perception of infectious danger (food items, conspecific)	Limiting the risk to contract an infection	Missing opportunities to feed, mate Reduced social interactions, cooperative behaviors	Perception of danger can vary with age, depending on experience Priorities might also change with age and the strength of the cost of missing mating opportunities increases as the risk of extrinsic mortality increases
Resistance	Immune response	Limiting pathogen proliferation Clearing the infection	Energetic cost of mounting the immune response Collateral damage if the immune response is misdirected or overreacting	Immune memory builds up during the ontogeny and then declines as T-cell clones get exhausted Thymic involution Chronic low-grade inflammation at old age
Tolerance	Immune regulation Repair of damaged tissues Renewal of cells destroyed during the infection Detoxification of toxins produced during the infection	Limiting the health/fitness reduction	Energetic costs of repair/renewal/detoxification Immune regulation can impair the effectiveness of the immune response to clear the infection Persistent infections	Reduced capacity to repair/renew damaged tissues and destroyed cells at old age Chronic low-grade inflammation at old age

burden while still minimizing the fitness cost) (Råberg et al. 2007). Resistance and tolerance are therefore two distinct but still important defense strategies that can be adopted in response to an infection (Råberg et al. 2009; Sorci 2013). Although resistance and tolerance can evolve independently from each other, they might also be linked if tolerance involves the down-regulation of immunity. Mice with a knocked-out cyclooxygenase pathway (which is the target of nonsteroidal anti-inflammatory drugs) experience less severe symptoms when infected with the influenza A virus compared to wild-type mice (improved tolerance), despite having higher viral titers in the lungs (reduced resistance) (Carey et al. 2005). With this respect, it is very important to understand how resistance and tolerance to infection can vary with age, since as mentioned above, the immune system goes through substantial changes during ontogeny (from birth to aging) (Table 5.1). If improved

tolerance involves a down-regulated immune functioning, senescing individuals might be expected to be less resistant but more tolerant to infection. Therefore, the relative importance of defense strategies may vary during the lifespan, from a resistant-oriented one at young age to a tolerant-oriented one at late age. Recently, this hypothesis has been tested in malaria-infected mice. Contrary to the prediction, this study found that mice at the onset of aging have both reduced resistance and tolerance to malaria infection compared to young individuals, suggesting that aging might involve a general deterioration of different components of defense (Sorci et al. 2021).

5.4 Trade-Offs Between Immunity, Defense Strategies, and Age-Dependent Disease

Life history theory tells us that investment into a given trait comes at the expense of investment into other functions. This resource allocation principle has been at the core of our understanding of the constraints or trade-offs that limit the expression of phenotypic traits. Although individuals might genetically differ in their resource allocation rule, environmental conditions obviously play a major role in how and when resources can be invested to a given function. The immune system is an extremely plastic function that rapidly responds to the environment and actually needs environmental input to properly function. Therefore, we expect that immune functioning should trade-against other individual physiological functions and life history traits according to the environmental conditions experienced and the resource allocation rule (Ardia et al. 2011; Keehen et al. 2021). Such trade-offs can involve traits that are expressed during the entire individual lifespan, from growth rate to early reproduction and longevity (Zuk and Stoehr 2002; Metcalf et al. 2020).

Phenotypic and genetic trade-offs between traits expressed at early and late ages determine why individuals age. Aging is a pervasive phenomenon in nature that is not restricted to humans or domestic animals (Nussey et al. 2013). Ample evidence has been accumulating showing that high investment into traits that are expressed at early ages induces an impaired expression of traits that are expressed at late age (Lemaître et al. 2015). Can investment into immunity contribute to explain such trade-offs? There have been several hypotheses that have been put forward to this respect. What makes the analysis of the effect of the immune system on the age-dependent expression of life history traits difficult is the complexity of the interactions between different environmental and intrinsic factors. To give an example of this complexity, mounting an appropriate immune response requires sufficient metabolic resources to produce the effectors which depend on food quantity and quality that individual acquire from the environment, but also requires the environmental input that educate the immune system to make the fundamental distinction between dangerous and harmless antigens. Therefore, immune protection at early age can shape further investment into late age life history traits following many

different pathways, and causal links (Fig. 5.4). To this respect, of particular interest is the permanent dialog that exists between the immune system and the huge diversity of environmental microbes that colonize the host's body, the microbiota. Commensal bacteria that live on the skin and on the mucosal layer of the oro-intestinal, respiratory, genital tracts play essential auxiliary functions that range from the metabolism to the regulation of the immune response (Cho and Blaser 2012; Gensollen et al. 2016; Schroeder and Backhed 2016; Ganal-Vonarburg et al. 2020). Although some exposure to microbial agents occurs prenatally (in the womb of mammals), the microbiota is mostly acquired during the early postnatal life, first during the delivery in mammals and then through the exposure to the environmental microbial diversity. During this stage of environmental acquisition of the microbiota, that can last for months or years in human infants, the immune system has to learn how to let such commensal fauna to establish while (i) avoiding overwhelming colonization and (ii) discriminating dangerous invaders. The modulation of the immune response is therefore an environmental factor that can have instantaneous but also delayed effects on host life histories. Epidemiological evidence suggests that the composition of the gut microbiota changes in the elderly in humans and correlates with age-associated pathologies (Claesson et al. 2012; O'Toole and Jeffery 2015). These findings have been corroborated by studies on animal models (Langille et al. 2014). Therefore, how the microbiota changes during the ontogeny might contribute to shape the trade-offs between life history traits and the susceptibility to infectious and non-infectious diseases during aging (Stiemsma and Michels 2018). To what extent these effects are mediated by the interactions between commensal and pathogenic organisms, and the host immune response is currently one of the topics at the forefront of research.

Investment into the immune function can also shape life history traits across generations. Such intergenerational trade-offs can take several forms. For instance, maternal transfer of antibodies in utero or *in ovo*, plus the provisioning of milk with IgA is supposed to provide protection to the offspring towards the prevailing pathogens to which the mother has been exposed (Navarini et al. 2010). As mentioned above, immune memory is built over time when individuals come across a variety of antigenic stimulations; therefore, newborns essentially lack immune memory. The transfer of maternal antibodies allows buffering the lack of immune memory of offspring. Maternal transfer of antibodies establishes a causal link between the maternal environment and the offspring phenotype. Transgenerational immunity is not a phenomenon restricted to vertebrates, since it has been shown to operate in insects and other invertebrates as well (albeit involving different immune effectors) (Roth et al. 2018).

5.5 Environmental Modulation of Early Immunity and Carry-Over Effects on Defense Strategies and Age-Associated Diseases

By now, it should be clear that the early activation of the immune response has the potential to have long-lasting effects on infection, health and fitness traits expressed at later ages, and that these effects can both be fitness-debilitating or fitness-enhancing. Here, we wish to give a short overview of the environmental factors likely to modulate the sign and strength of the relationship between early immunity and late infection/disease. Many environmental factors might actually be considered as good candidates for such a role. However, given their recognized potential as drivers of human-induced biodiversity loss at the global scale, we suggest that changes in resource availability, temperature, contaminant exposure, and infectious risk should be given priority. Changes in resource availability and infectious risk are tightly linked to the destruction of natural habitats, climate changes are exposing an ever-increasing number of species to novel thermal niches, and toxic wastes circulate in an unprecedented manner in all earth compartments (aquatic, terrestrial, atmospheric). Given the pervasiveness of these human-induced environmental changes, it seems primordial to understand if and how they can shape or alter the trade-off between defense against infection and other crucial life history traits at different life stages.

5.5.1 Trophic Resources

Given that maintaining the immune system and mounting an immune response requires energy, it is straightforward to expect that the availability of trophic resources (both quantity and quality) should modulate its expression. However, as already mentioned, the link between food availability and immune traits might reveal more complex than expected with some immune components that can even be up-regulated following food shortage. Adamo et al. (2016) conducted an experiment where caterpillars (fifth instar) of the moth *Manduca sexta* were exposed to three food treatments (high nutrition, low nutrition, and absent nutrition). While the food treatment had clear effects on energy-related traits (lipid, glucose), with insects in the high nutrition having the highest values and insects in the no nutrition the lowest ones, immune traits did not consistently vary among experimental groups, and caterpillars in the absent nutrition group even had higher levels of the total phenoloxidase activity. Interestingly, when looking at the expression of constitutive vs. inducible responses, the results showed that caterpillars in the no food group had up-regulated expression of four genes at the constitutive level. Upon stimulation of the immune response, absent nutrition insects failed to up-regulate immune genes.

Diet composition, in addition to the amount of food ingested, has also been shown to potentially shape immune functioning at early age. Choline is a nutrient that is involved in the synthesis of several essential biomolecules (phospholipids, lipoproteins, neurotransmitters). In mammals, offspring can get choline from maternal milk either as esterified (phosphatidylcholine) or unesterified (free choline) form. Phosphatidylcholine and free choline have different biochemical properties and metabolism. To investigate if different availability of the two forms of choline affects early immune function, Lewis et al. (2016) supplemented female rats with either free choline or phosphatidylcholine, and then explored how maternal nutritional status affected the immunity of the offspring. Offspring feeding from phosphatidylcholine-fed dams were found to produce higher amounts of several pro-inflammatory cytokines (IL-2, IL-6, IFN-γ) upon stimulation of splenocytes. Although these results neatly show that some micronutrients can drive the immune response towards a Th1 polarization, in an energy-independent way (rats from the two groups have similar body mass), they do not tell us to what extent this improves rat fitness at the short- or long-term. In agreement with these findings, a meta-analysis has reported intergenerational effects of parental diet on offspring immunity, including up-regulation of pro-inflammatory markers and down-regulation of anti-inflammatory effectors (Grueber et al. 2018). Given that all the studies included in the meta-analysis involved experimental design where offspring were fed control diets, this finding indicates a pervasive inheritance of nutrition-dependent immune functioning. Interestingly, such environmentally-driven inheritance seems to consistently skew offspring immune function towards a pro-inflammatory status, favoring offspring resistance, possibly at the expense of tolerance.

Given the complexity of the synergistic effects linking diet and immunity, ranging from the very direct effects of metabolic resources on immune cells and tissues to the indirect effect through the gut microbiota (Narayan et al. 2015; Knutie 2019; Ganal-Vonarburg et al. 2020), two key questions are particularly challenging to address. First, do the observed responses have an adaptive value? In other terms, to what extent immune adjustments that follow a change in the nutritional status of the host reflect the cost of an inappropriate diet or are they adaptive plastic responses allowing the organism to make the best of a bad job? Second, what are the long-term consequences of these early plastic adjustments? If these responses are adaptive, do they confer an immediate benefit with possible negative effects at later stages?

As already mentioned above, inferring the adaptive nature of diet-induced immune adjustment is particularly challenging, since up- or down-regulation might provide better protection or increased susceptibility depending on the pathogens likely to infect the host. For instance, in the experiment described above, *Manduca sexta* caterpillars in the high nutrition group had better survival prospect when infected with gram$^-$ and gram$^+$ bacteria (*Serratia marcescens* and *Bacillus cereus*), but similar survival when infected with the fungus (*Beauveria bassiana*), compared to the low nutrition group. Whether these differences in infection-induced mortality are due to immune-driven resistance and/or tolerance is, however, unclear. Whatever the underlying mechanisms, it seems clear that any selective benefit of nutritional modulation of the immune response will depend on the most prevalent pathogen

these caterpillars are likely to encounter and are therefore context-dependent. Moreover, the effect of resource availability on immune protection and susceptibility to infection should also be weighed by the concomitant effect that diet may have on other crucial life history traits such as growth, development time, or age at first reproduction.

What about the long-term immune-mediated effects of early diet? Arthropods are particularly prone for such studies, because of their relatively short lifespan. Kangassalo et al. (2018) exposed pupae of the greater wax moth (*Galleria mellonella*) to high or low diet and investigated the effect of these early-diet manipulation on pupae and adult immune functioning and life history traits. They found that the immune response (encapsulation rate) decreased between pupae and adults, but the rate of decline was much more pronounced in adults produced by larvae in the high diet group (and especially so in males). These results were accompanied by a concomitant lengthening of egg-to-adult developmental time and a reduction of adult body mass in the low diet group. Therefore, while poor early diet overall induced a fitness cost, male moths that experienced poor diet as pupae had better encapsulation response compared to moths from the high diet. Again, inferring the adaptive value of this long-term enhancement of immune response in poorly fed moths is far from easy. A possible explanation is that poor diet might be associated with environments with high infectious risk. In this case, there might be a reward from investing more into the immune function in poor environments. However, this rests on the assumption that poor diet correlates with increased risk of pathogen encounter over the whole moth life, which still has to be investigated. An alternative explanation might be that insects in the high diet group invested more in other life history traits (reducing developmental time and increasing body mass) at the expense of late immunity. This would imply that under good trophic conditions, investment into immune defenses might not be the favored strategic decision.

Early diet can also have consistent or idiosyncratic effects on different aspects of host defenses at the adult stage, and hosts might adopt different strategic defenses depending on the type of parasite/pathogen they are exposed to. The Cuban tree frog (*Osteophilus septentrionalis*) is the host of the gut nematode *Aplectana hamatospicula*. The nematode penetrates the host through the skin and then establishes in the intestine. Knutie et al. (2017) fed tadpoles of the Cuban tree frog with two food regimes (conspecifics or algae). After the metamorphosis, frogs from the food treatments were exposed to the nematode. Early diet affected both resistance and tolerance during adulthood, although the effect was idiosyncratic when decomposing resistance into the two major stages of the infection (penetration and establishment) (Fig. 5.5). Frogs that received an algae-based diet when tadpoles were more susceptible to the worm penetration, but once the worms had succeeded to enter the host the probability to establish in the gut was lower in frogs from the algae-based diet. Therefore, early diet affected resistance at the adult stage but the sign of the effect was different depending on the stage of infection. Frogs from algae-fed tadpoles also had a higher antibody-mediated immune response. Nevertheless, they were less tolerant in terms of infection-induced changes in body mass. Interestingly,

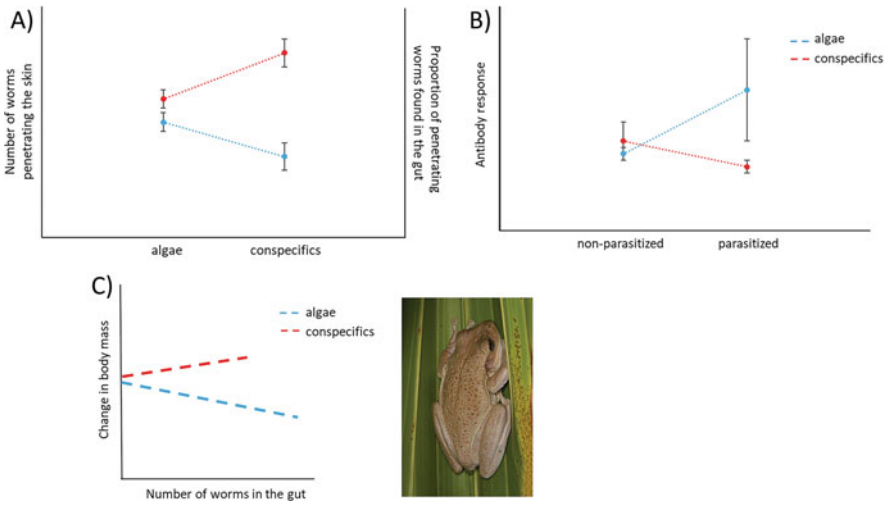

Fig. 5.5 Tadpole diet has carry-over effects on adult resistance, immunity, and tolerance to the infection in the Cuban treefrog. Tadpoles were fed with two food types (algae or conspecifics), after metamorphosis, frogs were exposed to the nematode *Aplectana hamatospicula*. (**a**) Frogs from algae-fed tadpoles had a lower resistance in terms of their capacity to avoid worm penetration (blue dots), but once the worm had penetrated the skin, they were more likely to avoid their establishment in the gut (red dots). (**b**) Frogs from algae-fed tadpoles mounted a higher antibody response upon infection with the nematode compared to conspecific-fed tadpoles. (**c**) Frogs from algae-fed tadpoles were less tolerant to the infection (steeper slope between change in body mass and infection burden) compared to conspecific-fed tadpoles. Redrawn and adapted for illustrative purposes from Knutie et al. (2017). Cuban tree frog (Image credit: Judy Gallagher, https://www.flickr.com/photos/52450054@N04/49766607846/, CC BY 2.0, https://creativecommons.org/licenses/by/2.0/)

all these long-term effects on immunity, resistance, and tolerance were independent from changes in the microbiota. Although diet had an effect on the microbiota, this was restricted to tadpoles, since there was no permanent change in the microbiota of adult frogs according to the tadpole food treatment.

Extreme environmental conditions can obviously impose strong priority rules, and immunity might be one of the functions that is shut down under very unfavorable conditions. To illustrate this, Muturi et al. (2011) exposed larvae of the mosquito *Aedes aegypti* to several environmental conditions that included a suboptimal food treatment and a starvation group. Emerging adult females were fed with blood containing the Sindbis virus. When looking at the expression of two genes encoding for antimicrobial peptides (cecropin and defensin) at the larval stage, starvation consistently induced a down-regulation of both genes. However, larvae in the suboptimal food group had an up-regulated expression of cecropin. At the adult stage, females that were exposed to starvation during the larval period had an up-regulated expression of defensin. Despite these nutritional-dependent immune adjustments, adult females from both the suboptimal food and starvation groups had higher susceptibility to Sindbis virus infection compared to the control group and

had a higher vector competence (higher capacity to spread the infection). As for the wax moth, suboptimal diet and starvation were consistently associated with increased development time, reduced adult female survival and body size. Therefore, while depleted food resources have consistent effects on the major life history traits, the immune modulation and the associated capacity to deal with an infectious threat appear to be stage-dependent.

5.5.2 Thermal Environment

Temperature is among the major components of climate change and ongoing thermal modifications are likely to impact biodiversity through the alteration of many biological processes and traits. Immune defenses and the outcome of host–parasites interactions should be explicitly integrated in mechanistic and trait-based approaches assessing species vulnerability to global change (Pacifici et al. 2015). The effect of temperature on immunity and its development is straightforward for ectotherms given that their internal temperature fluctuates with the thermal environment and affects all physiological processes and pathways. Indeed, insects can exploit the variation of their thermal environment to adjust their body temperature for optimal defenses against pathogens (Catalan et al. 2012). However, different physiological functions might have conflicting thermal optima, suggesting that preferred temperatures may vary according to the current priorities. As an illustration of the possible conflicting temperature optima between immune functions, Silva and Elliot (2016) found that when velvet bean caterpillars (*Anticarsia gemmatalis*) were reared under temperatures ranging from 20 °C to 32 °C, the expression of immune traits was increased (melanization), decreased (number of hemocytes), or did not vary (encapsulation) over the temperature range. Nevertheless, the fitness cost paid upon infection with *Anticarsia gemmatalis multiple nucleopolyhedrovirus* increased with rearing temperature as larval survival was reduced at high temperature. This suggests that in addition to the possible involvement of the immune system, high temperature negatively affects other physiological functions, resulting in deteriorating survival prospects.

An excellent example illustrating the need to have an integrative view of thermal preferences in infected animals comes from behavioral fever. As mentioned above, ectotherms can adjust their body temperature by altering their thermoregulatory behavior. For instance, lizards can bask to reach their thermal preference. Interestingly, this preference is altered following an infection. As for endotherms that produce a febrile response when facing a viral or bacterial infection, lizards have been shown to produce a so-called behavioral fever when infected (Vaughn et al. 1974). The adaptive nature of this variable thermal preference is manifold. Increasing body temperature can provide a thermal environment that deviates from the optimal temperature for pathogen proliferation (a direct defense mechanism). In addition to this direct effect, fever can also enhance several immune functions as shown in humans (Evans et al. 2015). If hyperthermia has beneficial effects in terms

of protection towards infectious diseases, why not always maintaining higher temperatures? Raising body temperature is associated with substantial metabolic cost, since an increase of 1 °C has been estimated to induce around 10% increase in metabolic rate (Evans et al. 2015). Moreover, as stated above, not all physiological functions perform the best at the same temperature and pathogens differ in their optimal temperature. Therefore, maintaining consistently high temperature would be more costly than raise the temperature only when needed. To this respect, we can easily draw a parallel between hyperthermia and the inducible immune response. Although constitutive immune defenses provide a sort of baseline level, inducible defenses are only deployed when the organism faces an infection.

As mammals, birds have an endogenous control of the body temperature. However, during the embryo development birds are exposed to environmental temperatures since egg temperature strongly depends on external temperature and parental incubating activity. Interestingly, egg temperature has been shown to have an effect on the immune response of the nestlings across a number of species. For instance, studying 22 bird species, Arriero et al. (2013) found that eggs incubated at higher temperatures produced hatchlings with better innate immunity. Experimentally incubating eggs at warmer temperatures also resulted in nestlings with better immune response in the wood duck (*Aix sponsa*) and the American robin (*Turdus migratorius*) (DuRant et al. 2012, Merrill et al. 2020).

Temperatures experienced during development have been reported to have carry-over effects on some immune traits (but not all) expressed during adulthood. *Pieris napi* butterflies emerging from larvae kept at 25 °C (corresponding to the upper value experienced by the species in the southern part of its distribution range) have a lower number of hemocytes compared to adults emerging from caterpillars kept at 17 °C (the mean temperature in the region where the experimental population was derived from) (Bauerfeind and Fischer 2014). However, prophenoloxidase (another important immune effector of insects) did not differ between thermal treatments.

Temperatures experienced during development are not necessarily the same of those experienced at other stages of life, and therefore any carry-over effect of developmental temperature may also depend on the temperature experienced later on. To address this question, Zhang et al. (2018) incubated zebrafish (*Danio rerio*) eggs at three temperatures (24, 28, and 32 °C), and upon hatching, fish from each temperature were distributed to one of the same three temperatures, in a fully-factorial design. Fish were then treated with an endotoxin (bacterial LPS) that can induce a potentially fatal septic-like syndrome. The findings revealed that prenatal (incubation) and postnatal (rearing) temperatures had different effects on fish mortality after LPS exposure. While mortality was the highest for fish that hatched from eggs incubated at the colder temperature (24 °C), within each incubation temperature, mortality increased with the rearing water temperature. Interestingly, the fact of experiencing the same temperature during the incubation and the post-hatching life never resulted in the highest survival (whatever the temperatures) (Fig. 5.6). This suggests that shifting from one thermal regime to another across life stages does not inflict an additional fitness penalty compared to homogenous temperature. In other terms, matching thermal environments across life stages is not associated with better

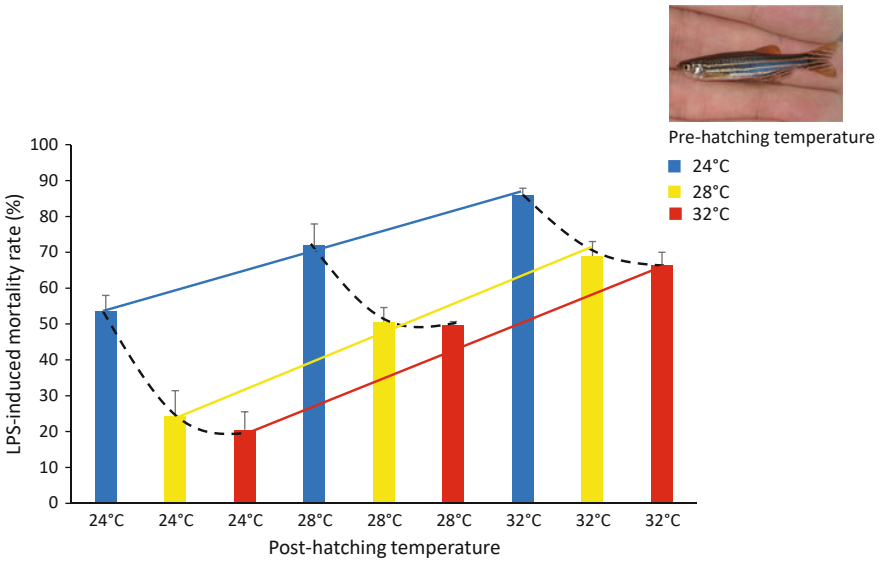

Fig. 5.6 Antagonistic effects of pre- and post-hatching temperature on LPS-induced mortality in zebrafish. Within each post-hatching temperature, larvae from eggs experiencing the lowest temperature had the highest septic-like mortality (blue bars) and mortality decreased as egg temperature increased (dotted curves). Within each pre-hatching temperature, larval mortality increased as long as they experienced warmer temperatures in their post-hatching environment (blue, yellow, and red lines). Therefore, contrary to the expectation of the matching environment hypothesis, mortality is minimized for high pre-hatching (32 °C) and low post-hatching (24°) temperatures. Redrawn and adapted from Zhang et al. (2018). Zebrafish (Image credit: Ffish.asia, https://upload.wikimedia.org/wikipedia/commons/2/2c/Zebradanio-P1219668.jpg, CC BY 4.0, https://creativecommons.org/licenses/by/4.0/)

fitness prospects in this particular system. Nevertheless, these findings indicate that temperatures experienced during different life stages can have idiosyncratic effects on fitness.

The previous example shows the importance of fluctuations in temperature experienced across life. Actually, temperatures fluctuate at a much smaller time scale and organisms usually face daily temperature fluctuations whose amplitude depends on habitat type and geographic region. However, experimental work has mostly neglected this daily variation in temperature and individuals are usually exposed to fixed values, representing mean temperatures. This might give unreliable results if organismal performance responds differently to fluctuation patterns occurring around low or high temperatures. In agreement with this view, Paaijmans et al. (2010) found that mosquitoes (*Anopheles stephensi*) raised either under a constant or a fluctuating temperature regime differed both in terms of their capacity to spread the agent of the rodent malaria (*Plasmodium chabaudi*) and their survival. Interestingly, the effect of the daily fluctuation depended on the mean around which temperatures were allowed to vary. Mosquitoes raised under a fluctuating regime around a low temperature (16 °C) harbored higher parasite numbers compared to mosquitoes

raised under a constant 16 °C temperature. On the contrary, at higher temperature (26 °C) daily fluctuations reduced parasite burden compared to constant temperature. These results are particularly important if we want to have better predictive tools to forecast the effect of global warming on the risk of emerging infectious diseases. Many questions remain however unresolved, including the carry-over effect of temperature fluctuation across early and late stages of parasite vectors. Another aspect that deserves more attention is to uncover whether improved vectorial capacity for one pathogen (e.g., a protozoan) under certain thermal conditions is traded-against the vectorial capacity for another pathogen (e.g., a virus).

5.5.3 Pollutions and Contaminants

During the last century, we have been witnessing an ever-increasing production (among others) of pesticides in intensive farming, drugs for human and animal health, and toxic wastes from industrial activities. As a consequence, contaminants (sensu *lato*) circulate now within virtually each compartment of the biosphere. Contrary to trophic resources and temperature, for which we can reasonably expect optimal values corresponding to maximum organismal fitness, once a concentration threshold is reached pollutants are expected to be associated with a negative fitness outcome. Beside contaminants, other types of pollution are also pervasive, as artificial light at night or noise, and may interfere with organismal performance through alteration of their physiological functions. The field of immunotoxicology has expanded during the last decade with the aim of uncovering if (and how) organisms can cope with these abiotic agents at different stages of their life.

Interpreting how pollutants affect the immune system can be particularly challenging because pollutants can i) directly impair the immune response; ii) damage host cells and tissues producing DAMPs that stimulate the immune response; or iii) be toxic to invading pathogens (which indirectly also affect the expression of the immune response). Functional responses, for instance in terms of the organismal capacity to deal with a controlled infection, are therefore needed to have an insight on the immune-mediated fitness consequences of contaminant exposure. Along this line, larvae of *Chironomus riparius* exposed to tributyltin, an organic pesticide used to protect wood, were found to have reduced hemocyte number while phenoloxidase activity was not affected by the pollutant (Lilley et al. 2012). However, life history traits such as development time and survival were consistently impaired in larvae exposed to the tributylin. *Galleria mellonella* caterpillars provided with food containing three different doses of nickel covering the range of concentration observed in polluted areas, had an improved encapsulation response for the two highest doses and higher phenoloxidase activity for the two lowest doses when compared to controls. However, this early up-regulation of the immune response did not provide any selective benefit since upon infection with the fungus *Beauveria bassiana*, larvae exposed to the highest dose of nickel suffered the highest mortality rate (Dubovskiy et al. 2011).

A set of two experimental studies on the *Xenopus laevis* provide an interesting insight into the influence of contaminants on immune function across life stages (Robert et al. 2018, 2019). Three weeks-old tadpoles were exposed to a mixture of 23 chemicals associated to unconventional gas and oil extraction (e.g., benzene, toluene) with three doses encompassing the exposure levels found in dense-drilling regions. After a three-week treatment, tadpoles were infected with the Frog virus 3. Infected tadpoles exposed to the highest pollutant dose suffered the highest mortality and harbored the highest viremia. Pollutants had a general down-regulating effect on the expression of pro-inflammatory cytokines in both kidneys and spleens, suggesting that the increased viremia and mortality might stem from a pollutant-associated immune suppression. Interestingly, there was a carry-over effect of early exposure to pollutants since when tadpoles were allowed to metamorphose and adult frogs were infected with the virus, they also paid a substantial cost in terms of increased viremia and infection-induced mortality. These findings therefore suggest that contaminants might enhance the susceptibility to infection with carry-over effects across life stages.

5.5.4 Early Infection with Pathogens and Parasites

Every host undergoes a permanent exposure to a diversity of microbial stimulations that range from harmless (mutualistic and commensal) to pathogenic interactions. Upon exposure to this wide range of stimuli, the immune system might or might not adopt the appropriate response and this obviously has fitness consequences both on the short- and long-term. As already mentioned in the previous sections, the first dichotomous branching decision the immune system has to take is between harmless and dangerous stimuli. Aggressive response to harmless stimuli can produce devastating autoimmunity as shown by several human diseases, weak responses to dangerous pathogens can result in overwhelming pathogen proliferation. Even when the immune system can reliably target dangerous stimuli, it still has to finely tune the intensity of the response as to avoid immunopathology. The combined effects and the finely-tuned balance between activation, regulation and memory are therefore essential features of an effective immune response.

Antigenic stimulation in early life contributes to shape the repertoire of "memory" cell lineages that can be mobilized upon future exposure to the same or similar antigens. The idea that immunity has memory was initially restricted to vertebrates (and their antibody producing B-cells). However, during the last decades evidence is mounting showing that the "simpler" immune system of invertebrates has the capacity to memorize previous antigenic exposure (Critchlow et al. 2019). This phenomenon has been called immune priming and its rationale is essentially identical to vaccination (Trauer and Hilker 2013; Tate et al. 2017). Early exposure to a diversity of antigens sets the memory that allows a rapid response if the same (or close enough) antigens are encountered again at later life stages. Therefore, immune memory provides a benefit as long as the individual likely encounters the

same pathogens during its lifespan. For instance, when *Anopheles gambiae* larvae are infected with the bacterium *Escherichia coli*, they produce a response that confers a protection when the adult mosquitoes are subsequently re-infected with *E. coli* (Brown et al. 2019). Adult mosquitoes emerging from infected larvae had an up-regulated expression of several immune functions and harbored lower bacteremia. Interestingly, infection at the larval stage conferred some cross-protection, since even adults emerging from larvae infected with *Enterobacter* sp. and *Staphylococcus aureus* were protected against subsequent infection with *E. coli*.

Benefits of immune memory are obvious for vertebrates, which have specific memory B-lymphocytes. C57BL/6 mice infected with mousepox virus (ECTV) may suffer from severe mortality and previous exposure to vaccinia virus (another orthopoxvirus) confers protection towards ECTV-induced mortality. This protection can also arise from the maternal transfer of memory immune effectors, since females treated with the vaccinia virus produce offspring that are protected if they are infected with ECTV when adults (Navarini et al. 2010). These results illustrate how the absence of exposure to infection during early life can have long-term negative fitness effects by maintaining susceptibility to novel pathogens.

Cross-reactivity is an important associated benefit of immune priming and "vaccination." Indeed, as shown above, if different pathogens share similar antigenic epitopes, exposure to one of them can confer a (partial) protection even when the host encounters other pathogens. However, under certain circumstances, early infection (exposure) can also enhance the risk of contracting other infectious diseases. For instance, although bacterial infection of *Anopheles* larvae protected towards bacterial infection occurring at the adult stage, mosquitoes emerging from infected larvae had increased susceptibility to the infection with the protozoan *Plasmodium yoelii* (Brown et al. 2019). On the same line, Sadd and Schmid-Hempel (2009) showed that when queens of the terrestrial bombus (*Bombus terrestris*) are infected with the bacterium *Arthrobacter globiformis*, they produce workers that are protected from bacterial infections but are more susceptible to infection with *Crithidia bombi* (a protozoan parasite). The reasons for these conflicting effects are manifold. For instance, in vertebrates, antigen-presenting cells may express different MHC molecules that bind to specific pathogen epitopes. Therefore, depending on the type of MHC molecules expressed, individuals might be resistant to some pathogens and susceptible to others (Loiseau et al. 2008), a form of antagonistic pleiotropy. More generally, signaling molecules that orchestrate the immune response (such as cytokines and chemokines) are known to have synergistic or inhibitory effects (Sorci et al. 2017). For instance, activation of the Th1 response following viral (intracellular) infection is characterized by the production of Th1 cytokines (IL1-β, IFN-γ) that have inhibitory effects on Th2 cytokines (IL-4, IL-5, IL-13), and vice versa. Accordingly, previous infection with a helminth parasite can enhance subsequent infectious risk with microparasite by polarizing the immune response (Ezenwa and Jolles 2011).

Early infection may also have effects on fitness related traits expressed at late age that do not necessarily involve increased (or decreased) susceptibility to infection. Infection during early life can have long-term effects on neuronal development and

several behavioral traits (Bilbo and Schwarz 2012; Grindstaff 2016). For instance, great tit nestlings (*Parus major*) raised in nests with hen fleas (*Ceratophyllus gallinae*) produce shorter songs once adults which has negative fitness consequences both in terms of intra- (male-male competition) and inter-sexual (female choice) selection (Bischoff et al. 2009).

Similarly, it has been suggested that early infection and the associated activation of the inflammatory response might predispose individuals to higher risk of inflammatory diseases at later ages, potentially resulting in increased adult mortality (Finch and Crimmins 2004). This hypothesis stemmed from the finding of positive within-cohort correlation between early and late mortality in pre-industrial human populations (Finch and Crimmins 2004). Although subsequent studies using other human populations failed to reproduce these results, the hypothesis stimulated further experimental work conducted under controlled laboratory conditions, allowing to better inferring the possible causal link between early infection and actuarial senescence (Fig. 5.7). In agreement with the hypothesis, Khan et al. (2017) showed that *Tenebrio molitor* beetles facing an early inflammatory insult had higher age-dependent mortality risk and an accelerated actuarial senescence. Interestingly, the age-dependent increase in mortality was presumably due to an overreacting immune response, since beetles treated with RNAi inhibiting phenoloxidase had a better survival prospects. Similarly, laboratory mice infected with the gut nematode *Heligmosomoides polygyrus* at young age have accelerated mortality at old age compared to sham-infected individuals (Guivier et al. 2018). *Heligmosomoides polygyrus* does not induce any direct mortality in lab mice (unless high infective doses are used), and the infection is naturally cleared by the host after few weeks/months (depending on the host genetic background). Therefore, the increased mortality at late age does not arise because of a direct effect of the parasite (at that moment, the infection has been cleared since longtime) but indeed reflects a carry-over, negative consequence of early infection. Even seemingly benign parasites that do not exert any direct mortality cost can nevertheless incur delayed fitness costs on their hosts through early immune-mediated effects. Uncovering the generality of these delayed costs clearly requires further work, since not all studies have reported evidence for such accelerated senescence in early-infected individuals. For instance, lab mice infected with *Plasmodium yoelii* when young had similar values of inflammatory markers (CRP) at old age, similar reproductive output and similar age-dependent survival to control mice (Lippens et al. 2018).

5.6 Conclusion and Future Directions

Evidence supporting the view that environmental conditions experienced during early life have long-lasting effects on individual performance has been accumulating during the last decades. Virtually every aspect describing the environment faced at young age, from trophic resources to the infectious risk, has the potential to permanently shape future life history traits and fitness. This occurs through

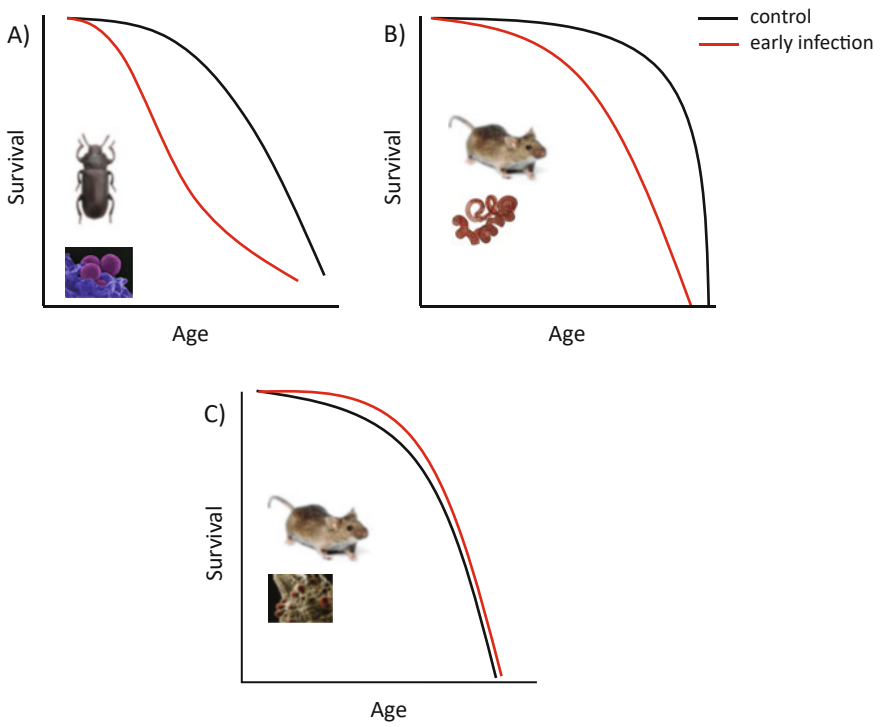

Fig. 5.7 Effect of early infection on actuarial senescence. We report survival curves of controls and individuals that had been exposed to an infectious insult in early life. (**a**) *Tenebrio molitor* that were infected with *Staphylococcus aureus* in early life have shorter lifespan than controls. (**b**) Similarly, laboratory mice infected with the nematode *Heligmosomoides polygyrus* at young age have reduced longevity. Here, the increase in mortality occurs once the infection has been cleared, showing that the accelerated actuarial senescence is a delayed cost of early infection, rather than a direct effect of parasite exploitation. (**c**) On the contrary, laboratory mice infected with the protozoan *Plasmodium yoelii* at early age have similar survival prospect of control individuals and age at the same rate. The three panels are redrawn and adapted from Khan et al. (2017), Guivier et al. (2018), and Lippens et al. (2018), respectively. In each of these studies, several experimental groups were tested. Here, we only present control and early infected groups, for illustrative purposes. *Tenebrio molitor* (Image credit: Stanislav Snäll, https://naturforskaren.se/species/3187f49c-3838-4afa-b39d-b44e9287fcaf, CC BY 3.0, https://creativecommons.org/licenses/by/3.0/); *Staphylococcus aureus* (Image credit: National Institutes of Health, https://commons.wikimedia.org/wiki/File:Neutrophil_MRSA_II.jpg, public domain); house mouse (Image credit: National Institutes of Health, https://upload.wikimedia.org/wikipedia/commons/8/8f/Mouse_white_background.jpg, Public Domain); *Heligmosomoides polygyrus* (© Joel Bowron, with kind permission); *Plasmodium yoelii* (© Hilary Hurd, with kind permission)

interactions between environmental features and physiological functions that undergo a developmental/maturation phase during ontogeny. Here, we focused on one of such functions, the immune system, because it meets all the requirements to mediate environmentally-driven trade-offs over the whole individual lifespan. To this respect, we tentatively draw a parallel between the DOHaD hypothesis and what

we might call the Immune Origin of Health and Disease (IOHaD) hypothesis. We postulated that early environmentally-driven shaping of the immune system sets a program that might account for future susceptibility to infection and immune-mediated diseases, ultimately affecting organismal fitness. We identified some key environmental traits likely to play such a role and discussed some of the evidence that has been published so far on the immune-mediated carry-over effects on infection, disease, and fitness. Overall, the take-home message seems to be that the complexity of the network of interactive effects between environment, immunity, defense strategies, disease, and fitness-linked traits over the individual lifespan prevents having a unique general prediction of how early effects of the environment on the immune system shape late age fitness. Context-dependent effects seem instead ubiquitous. Similarly, idiosyncratic effects of different environmental factors make impossible to unambiguously predict how early environment will shape immune-mediated health and disease in late life. On the one hand, this might appear as a disappointing conclusion, but on the other hand, it might stimulate further work trying to better elucidate these complex interactions and possibly making sense of the tremendous variation that is commonly reported in studies focusing on environmentally-driven immune effects over ages. A first step in this direction might be to use quantitative analytic tools (e.g. meta-analysis) to uncover subtle patterns that might not be easily spotted when using a qualitative perspective approach, as done here. A further development of theoretical models might also help to have more refined predictions on how and when we should expect early environmental conditions to increase or decrease investment into immune defenses according to the prevailing infectious risk and the possible late-life effects. Building such models is certainly not an easy task because of the intertwined links between multiple biotic and abiotic compartments with different age-dependent dynamical properties. To this respect, for the sake of simplicity, we only considered isolated environmental traits that have been reported to have an effect on immunity during development (e.g., food, temperature, infection). However, it is clear that environmental conditions are better described by interactive rather than additive effects. For instance, raising temperature can have a direct effect on organismal physiology and indirect effects through the alteration of other environmental compartments (e.g., quality and quantity of available resources, presence and abundance of vectors/pathogens/parasites, diversity, and abundance of competing species). Although experimental work is needed to infer the causality of effects, the reductionist approach associated with laboratory experiments might result in overly simplistic environments that are never encountered in natural conditions. This further impairs the reliability of our current predictive power. Future work should also explicitly consider how the effect of environmental conditions depends on the host genetic background. On the one hand, assuming that all genotypes will equally respond to environmental challenges seems unrealistic. On the other hand, testing for genotype x environment interactions across different life stages is a daunting task in most natural systems.

We are witnessing dramatic and unprecedented environmental changes induced by human activities. Given their impact on biodiversity, it is important to better

understand how environmental changes affect infectious risk through immune-mediated pathways. As wildlife species, human populations have also experienced profound changes in their environment during the last century. The increase in urban lifestyle that is occurring worldwide, associated with sedentary habits and increased consumption of processed food with high fat and sugar contents has rapidly produced a set of novel environments compared to the prevailing conditions experienced by humans during their evolutionary history. This mismatch is actually recognized as one of the principal reasons for the emergence of non-communicable disease epidemics that include obesity, diabetes, and immune-associated pathologies (Sorci et al. 2016). Improved sanitation, food security, medical interventions, economic development that occurred during the twentieth century have resulted in a considerable lengthening of human lifespan (although huge disparities still exist between populations depending on their socio-economic status). Lifespan lengthening has, nevertheless, also opened the window for human pathologies that are expressed at ages where the strength of natural selection is too weak to operate. Many of these diseases have an immune-related etiology, and often the causal link with the immune system can be traced back to our infancy. For instance, it is now well established that limited exposure to the environmental diversity of commensal microorganisms that colonize our body during infancy can have permanent effects on the risk to suffer from immune disorders (e.g., allergies, metabolic syndromes, inflammatory diseases; Ege et al. 2011; Hanski et al. 2012). Therefore, while the study of early environmental conditions on the immune-mediated health/disease trajectories in wildlife species is still in its infancy and the available results provide somehow mixed results, human studies have delivered more consistent findings. Of course, wildlife species, overall, face more complex environmental conditions compared to humans. One of the next challenges will be to uncover whether such complexity provides a buffer protecting towards immune-mediated pathologies and whether wildlife exposed to anthropic activities will suffer from fitness-debilitating immune-driven pathologies as long as their environment changes.

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Chapter 6
Early Life Nutrition and the Programming of the Phenotype

Katherine L. Buchanan, Alizée Meillère, and Tim S. Jessop

Abstract Early developmental nutrition profoundly influences phenotypic trajectories and affects adult morphology, physiology, behaviour, longevity and fitness across taxa. During early life, the interplay amongst quantitative (e.g., caloric intake), qualitative (macro- and micronutrient balance) and temporal (nutrient restrictions, predictability) aspects of early diet imposes constraints, as animals seek to balance their nutritional demands to optimise their development. The physiological mechanisms controlling food intake are established during early development, and environmental conditions at this time may play a role in determining long-term fitness. For vertebrates, the physiological axis regulating food intake interacts with the physiological response to environmental stressors and this may induce long-term programming of feeding behaviour and the adult phenotype. The diverse phenotypic and fitness consequences across ontogeny are dependent on both the magnitude and duration of 'non-optimal' nutrition during early development, as well as the degree of developmental plasticity in trait development. During early development, nutrition directly, or indirectly, affects cellular proliferation, migration, and differentiation. At this time, the capacity for compensation for periods of nutritional restriction is reduced and there are critical developmental windows of increased susceptibility, with potential for irreversible phenotypic plasticity. Such trait-specific critical windows for nutritional sensitivity may have adaptive explanations, favouring early life plasticity in relation to both environmental cues and environmental predictability. Whether responses to nutritional deficiencies represent developmental constraints or adaptive responses for future environmental conditions is in many cases unclear. Furthermore, transgenerational impacts of early life diet are documented in a small range of species, but the ecological and evolutionary relevance of these effects and capacity for selection on the underlying mechanisms remain uncertain. Future research that seeks to better detail the mechanistic understanding of how complex nutritional trade-offs alter developmental trajectories to

K. L. Buchanan (✉) · A. Meillère · T. S. Jessop
Centre for Integrative Ecology, School of Life and Environmental Sciences, Deakin University, Geelong, VIC, Australia
e-mail: kate.buchanan@deakin.edu.au

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specifically influence fitness offers considerable potential to benefit humans and animals, across diverse environmental settings.

6.1 Introduction

The 18thC French lawyer and gastronome Anthelme Brillat-Savarin famously once wrote, 'Dis-moi ce que tu manges, je te dirai ce que tu es.': *Tell me what you eat and I will tell you what you are* (Brillat-Savarin 1826). The concept that environmental influences such as diet determine our current state and body composition, developmental processes, rates of senescence, and ultimately our survival and reproduction, is far from new. However, the objective quantification of the complex, multidimensional reaction norms relating diet to development has only started in much more recent years (West-Eberhard 2003; Partridge et al. 2005; Simpson and Raubenheimer 2012). From the perspective of biomedical science, the recognition of the important role diet plays in determining adult health and disease susceptibility (Gluckman and Hanson 2006) has grown in tandem with the increased health and economic burden associated with increased rates of obesity in the developed world (Simpson and Raubenheimer 2012). Examining why people choose the burger over the salad has ultimately provided important insights into how selection on physiological and developmental processes has driven dietary intake (Simpson and Raubenheimer 2012).

By definition, any book chapter addressing the complex interactions between the early nutritional landscape and adult phenotype has to pick some robust highlights, whilst drawing conclusions about the broader relevance. Humans are of course the best-studied, but least controlled study organism, and yet an array of early dietary influences have been documented to affect adult phenotype, including absolute caloric intake, macro and micronutrient content, the variability and predictability in food availability, as well as the severity and duration of any restrictions (Langley-Evans 2015). Comparative experiments have addressed some of the underlying effects through careful manipulations demonstrating the direct impact of early life diet on developmental rates and patterns, growth rates and morphology, and subsequent physiology and behaviour (Gilbert 2001; McMillen and Robinson 2005; Pechenik 2006; Dmitriew 2011; Moran et al. 2021). Evolutionary ecologists have employed an array of model organisms to address how when and why early nutrition as a key environmental variable drives phenotypic plasticity (Rion and Kawecki 2007; Van Buskirk and Steiner 2009; Kasomovic 2013). This has led to studies quantifying the potential for adaptive physiological responses to early life diet and the impacts on individual fitness, in part driven by considerable interest in the effects of caloric restriction on ageing (English and Uller 2016; Simpson et al. 2017; Cooper and Kruuk 2018). Understanding the proximate effects of early nutrition on development, behaviour, and cognition has also provided important insights into the drivers for how dietary intake shapes adaptive development in wild animals (Crespi and Unkefer 2014). Early life diet can determine dietary choices in later life, thereby reinforcing the effects of early developmental programming (Monaghan 2008).

Furthermore, in the last 20 years, recognising the transgenerational impacts of diet on developmental patterns across generations has attracted interest in understanding the underlying selective mechanisms (Bateson et al. 2004).

The literature documenting the impacts of nutrition on growth and development is vast; this literature draws from aquaculture, agricultural production, biomedicine, through to animal physiology and then conceptually further into ecology and evolutionary biology. Here, we make minimal use of the biomedical literature, focusing on insights drawn from evolutionary ecology. In seeking to draw some general conclusions about how selection impacts the interactions between early nutrition and development, we focus on studies of nutritional manipulations during early development using wild animal models that have sought to quantify adaptive responses. Nutrition can vary along multiple axes and here we refer to caloric restriction as undernutrition—i.e., a shortfall in the required energetic supply at a given time in development. This is in contrast to malnutrition, which is a shortfall in some aspect of the balance of nutrient content of the diet which optimizes development. Experimental manipulations of *dietary* or *nutritional restriction* can impact on both caloric intake and nutritional content, whereas dietary manipulations to restrict specific nutritional components can target the specific impact of particular essential micro and macronutrients. Furthermore, studies of *dietary* or *nutritional stress* which manipulate the temporal availability of food and its predictability, by definition can address whether and how the animal deviates from an optimum developmental trajectory, as well as the physiological control mechanisms which mediate the impact. Where possible, we have differentiated between these different approaches to manipulating early nutrition. However, it would be reasonable to note that the published literatures uses some of these terms interchangeably. We aim to briefly review the impact of early nutrition on development, behaviour, senescence, reproduction and longevity, and the potential for transgenerational impacts of nutrition to identify targets for selection. We focus primarily on vertebrates, with an avian emphasis, whilst drawing on relevant insights from the invertebrate literature, where the shorter generation times have allowed effective experimental manipulations. In the first part of this review, we address the proximate mechanisms underlying the impact of nutrition on development. We highlight the impact of early diet on developing morphology and physiology, which interact to influence the drivers for future nutritional intake. We discuss selection to optimise macronutrient intake and the role of micronutrients. In the second part of the chapter, we address the implications of nutritional change for developmental plasticity. We seek to identify whether there are consistent critical and sensitive windows when animals may be more vulnerable to the effects of nutritional restriction and, what developmental factors might determine such susceptibility. Plasticity driven by early nutrition comes in many forms and here we discuss the evidence for selection on its metabolically-driven consequences. Finally, in the third part of the chapter, we discuss the transgenerational impacts of early life diet. In assessing the evidence for adaptive programming through early nutritional experience, we discuss the ultimate consequences of early life diet for individual fitness and where adaptive phenotypic changes may occur.

6.2 Proximate Mechanisms Affecting Development and Phenotype

6.2.1 Effects of Developmental Diet on Adult Morphology

In arthropods, both caloric restriction and restrictions to diet quality lead to altered development rates, adult body sizes and condition (Nylin and Gotthard 1998; Boggs and Niitepold 2016). *Drosophila melanogaster* has been a model organism for the study of early nutrition on development for over 100 years, including determining the impacts of caloric restriction, suboptimal diets, and the predictability of nutritional availability (Flatt 2020; Rehman and Varghese 2021). For example, caloric restriction during early larval development causes reduced adult weight, faster development and reduced fecundity, but in doing so produces adaptive changes including increased fat deposition and starvation resistance in adult flies (Rehman and Varghese 2021). Because larger animals tend to have relatively greater reproductive capacity (Blanckenhorn 2000), early life diet can determine fecundity, moderated by complex sex-specific relationships between fitness and body size (e.g., Gray and Eckhardt 2001; Kaspi et al. 2002; Boggs and Freeman 2005; Kasomovic 2013; Johnson et al. 2014). The impact of diet on fitness can result from changes to growth rates and adjustments in allocating limited resources (Nylin and Gotthard 1998) or development times (Fig. 6.1). Faster growth rates are presumed desirable, but may come with associated physiological costs (Metcalfe and Monaghan 2001), as well as increased risks of predation or parasitism (Nylin and Gotthard 1998), which may change dietary preferences (Hawlena and Schmitz 2010). In some species, there is some evidence that the degree of plasticity varies with resource predictability (Leimar et al. 1994). Adaptive trade-offs include morphological trade-offs; for example the body size of both male and female Mormon fritillaries (*Speyeria mormonia*) is reduced under larval dietary restriction (Boggs and Niitepold 2016). However, head size is conserved, suggesting that morphology of feeding apparatus, sensory systems or neural function may be protected. A range of experimental nutritional stressors impacts spiderling growth in wolf spiders (*Pardosa prativaga),* although compensatory growth allows attainment of adult size, driven by phenological pressures (Jesperen and Toft 2003), albeit with possible costs in later life (Metcalfe and Monaghan 2001).

Larval diet is also fundamentally important for determining adult morphology in anurans, which also show a high degree of phenotypic plasticity (Kupferberg 1997). Diet quality and absolute food intake affect tadpole body size (Kupferberg 1997; Alvarez and Nicieza 2002). But this is thought to be partly because of the role that dietary protein levels play in determining thyroid function, which plays an important role in determining the onset of metamorphosis (Kupferberg 1997). In songbirds, the zebra finch (*Taeniopygia guttata*) has been used as a model for determining the effects of nutritional restriction on growth, development and physiology (Spencer et al. 2003; Zann and Cash 2008; Kriengwatana et al. 2014). Both direct (Spencer et al. 2003) and indirect (Verhulst et al. 2006) nutritional restriction during early

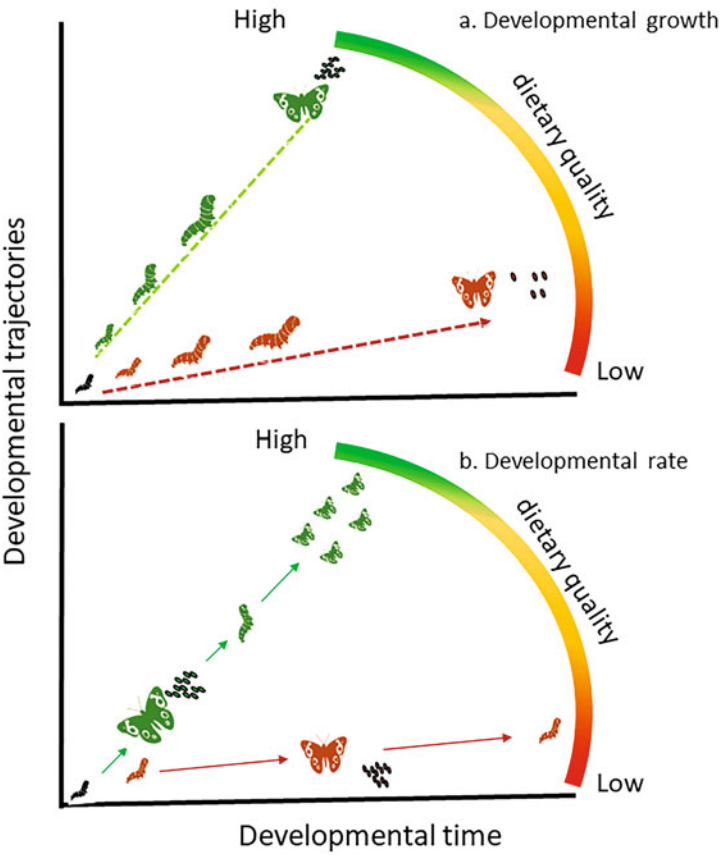

Fig. 6.1 Variation in the quality of nutritional intake can affect rates of (**a**) growth or (**b**) development, whilst dietary quality varies in multi-dimensions. (**a**) Dietary quality affects the speed of growth, such that individuals consuming a higher quality diet grow more quickly and may reach a larger body size and/or produce more offspring. (**b**) Diet quality affects development rate, with higher quality dietary intake enabling faster development. In both scenarios higher diet quality leads to increased fitness. Whilst it seems likely that these mechanisms are not mutually exclusive, the general impact of these effects at the population level will depend in part on the seasonal window available for development and reproduction

nestling life causes a reduction in growth rates. Several studies have attempted to identify the sensitive developmental windows by temporally partitioning the effects of diet during different periods of early development using the zebra finch as a model (Criscuolo et al. 2008; Krause et al. 2009). During the nestling period restricted caloric or protein intake causes reduced growth in mass, tarsus and wing length, with compensatory growth occurring when dietary quality is increased, such that body mass and tarsus length are usually indistinguishable from control birds as adults (Criscuolo et al. 2008; Honarmand et al. 2010). In contrast, adult skeletal size seemed to be largely resistant to periods of dietary restrictions in early life (Spencer

et al. 2003; Honarmand et al. 2010; Kriengwatana and MacDougall-Shackleton 2015), suggesting strategic allocation of available resources occurs. Body composition was unaffected by nutritional restriction in early life in song sparrows (*Melospiza melodia*) (Schmidt et al. 2012). However, fledgling and adult body composition were affected by early life dietary restriction in zebra finches (Kriengwatana and MacDougall-Shackleton 2015), reducing mass and lean mass, but not body fat stores. Such outcomes may serve to buffer the effects of temporary caloric restriction, similarly to the effects seen in adult birds exposed to unpredictable food availability (Witter et al. 1995). The potential for adaptive programming from early life conditions has also been tested, to address whether individuals reared under challenging conditions fare better when meeting these conditions again as adults. For example, zebra finches exposed to reduced dietary protein early in life tend to lose more mass during a short nutritional restriction as adults (Krause et al. 2009), although the adaptive significance of this response is unclear.

In mammals, embryonic growth is dependent on maternal supply of nutrients through the placenta and compromised maternal nutrition at this stage leads to complex trade-offs in resource allocation, mediated by placental mechanisms which control allocation. Studies of maternal diet in rodents confirm that either caloric excess or restriction lead to a predisposition to adiposity, neural inflammation, altered HPA function, metabolism and hyperphagia in their adult offspring (Schenk et al. 2008; Lumeng and Saltiel 2011). In mice (*Mus musculus)*, restricted maternal protein levels during pregnancy lead to a reduction in maternal body and placental weight early in pregnancy, but with embryonic skeletal and brain development less affected, and buffered during periods of compromised maternal nutrition (Gonzalez et al. 2016). This study also suggests that the junctional zone of the placenta serves as a sensor for maternal nutrition (Gonzalez et al. 2016). Postnatal skeletal growth rates in rats are reduced under protein restriction, such that individuals grow for a longer time, but still attain smaller adult skeletal sizes (Reichling and German 2000). Interestingly, whilst organ sizes were buffered from the effects of protein restriction, relative eye and brain mass were larger for protein-restricted individuals suggesting adaptive reallocation of resources (Reichling and German 2000). Indeed, there is a vast literature on the impacts of poor pre- and postnatal nutrition on mammalian growth, morphology and condition within the biomedical literature, which is beyond the scope of this current review.

Ontogenetic allometry refers to the relative growth rates of different body parts during early development, influenced by genetic and environmental factors, whilst there are numerous examples of how nutrition can impact adult phenotype, particularly in invertebrates (Nijhout and McKenna 2019). Wing loading in Mormon fritillaries is significantly reduced in both sexes by larval food restriction, whilst aspect ratio is conserved (Boggs and Niitepold 2016), suggesting that larval dietary restriction results in changes to body allometry, which maintain the ability to disperse and feed effectively. Alterations to wing size in response to larval dietary restriction have been shown in other Lepidopteran species, including the speckled wood butterfly (*Pararge aegeria*) (females only) (Pellegroms et al. 2009) and the

long distant migrant monarch butterfly (*Danaus plexippus*) (Johnson et al. 2014), with implications for migration success. Adult insects do not grow, so any diet impacts on morphology can only occur during larval stages. The impact of nutritional restriction on development may be characterised by a series of trade-off 'decisions' concerning resource allocation and yet we know rather little about the flexibility in resource allocation, particularly in vertebrates. There are two ways in which nutrition can potentially influence organism allometry (Nijhout and German 2012). Organism allometry might be directly altered through nutritional resource allocation, impacting on the growth rate of different parts of the body relative to each other. Alternatively, nutrition may indirectly influence the underlying tissue or organ-specific mechanisms, such as growth factors, developmental hormones or receptor expression and placement (Nijhout and German 2012). Parts of the developing body compete for resources, although the extent to which this occurs is poorly understood particularly in vertebrates (Gawne et al. 2020). Endothermic vertebrates (and some ectotherms (Frydlova et al. 2020)) show determinate growth (Sebens 1987), meaning the potential for nutrition to impact on allometric relationships throughout life is reduced in comparison with most poikilothermic vertebrates. The inherent trade-offs in body components are determined according to the timing of development and nutritional restriction (Nijhout and Emlen 1998). However, theoretical predictions suggest that nutritional limitations may benefit trade-offs between cellular demands during ontogeny (Gawne et al. 2020). Consumptive competition occurs when cells take up limited resources (metabolic fuels or charged molecules) at different rates, resulting in differences in cellular competitive abilities and theoretically tissue growth rates (Gawne et al. 2020). Such processes are thought to underlie differences in cellular recruitment from such diverse functions as neuronal competition and consequent memory formation in mice (Han et al. 2007), to competitive allocation of limited resources allocated to the formation of wing morphology in Diptera (Ferreira and Milán 2015) or Lepidoptera (Nijhout and Emlen 1998).

6.2.2 *Effects of Developmental Diet on Adult Behaviour*

Poor nutritional conditions in early life are hypothesised to have long-term effects on adult behaviour by altering neural development or function, adaptively reallocating resources and reprograming development to maximize fitness despite such challenges (Buchanan et al. 2013). Changes to the nutritional environment alter the cost-benefit trade-off of survival and reproduction (see Sect. 6.4.2) resulting in changes to sexual signalling in arthropods, fish and birds (Candolin 2000; Hunt et al. 2004). Male field crickets (*Teleogryllus commodus*) reared on high-protein diets invest more in calling behaviour and consequently show reduced survival (Hunt et al. 2004). However, in decorated crickets (*Gryllodes sigillatus*) male calling is affected by both juvenile and adult diet, whilst the exact nature of how diet impacts on trade-offs between reproductive investment and survival varies between the sexes

(Houslay et al. 2015). In songbirds, nutritional restriction during early life has been hypothesised to result in compromised adult song production due to the historical window for neural development which may compromise signal production (Nowicki et al. 2002). This hypothesis has been extensively tested experimentally (Buchanan et al. 2004; Schmidt et al. 2013; Kriengwatana et al. 2014), particularly in the zebra finch in relation to song learning (Bell et al. 2018) and production (Kriengwatana et al. 2014), but also in a range of other songbird species (Schmidt et al. 2014; Yamada and Soma 2016; Magoolagan et al. 2018). As predicted in the original hypothesis (Nowicki et al. 2002), there is evidence that the direct effects of developmental stress on song development are mediated through altered neural development within the song control nuclei, affected directly or indirectly through corticosterone (Buchanan et al. 2004; MacDonald et al. 2006; Newman et al. 2010; Honarmand et al. 2016; but see Buyannemekh et al. 2020).

Nutrition affects acoustic signalling outside of a developmental context. Aside from avian song learning, there is considerable evidence that nutrition affects song output around the time of production (Grieg-Smith 1982; Ritschard and Brumm 2012), but much less evidence that diet affects song structure, once established (Ritschard and Brumm 2012; Yamada and Soma 2016). Dietary antioxidant intake has been reported to enhance undirected song activity in the zebra finch, during a period of decreasing song rates due to reduced photoperiod (Casagrande et al. 2016). Male European starlings (*Sturnus vulgaris*) sing less, using shorter, simpler songs when exposed to unpredictable food supply, but this effect seems to be in part mediated through the buffering of increased male body mass (Buchanan et al. 2003). Such results suggest that juvenile diet-related alterations to adult signal production are not purely mediated by energetic restriction, but strategic reallocations (Hunt et al. 2004). Indeed, a recent meta-analysis considering multiple types of behavioural sexual signals confirms that individuals invest more in sexual signalling when they are in better condition (Dougherty 2021). In terms of the effects of nutritional stress on female song preferences, in the European starling there is some evidence that exposure to unpredictable food supplied affects auditory discrimination in females (Farrell et al. 2016). However, nutritional restriction during the nestling phase does not impact female song preferences in zebra finches (Woodgate et al. 2011).

Nutritional supply during early development can affect other cognitive traits, including spatial memory (Buchanan et al. 2013). For honey bees (*Apis mellifera*), pollen contains a range of essential nutrients, and access to pollen during the larval phase affects the ability of adult workers to subsequently convey accurate information about the location of food sources to other colony members (Scofield and Mattila 2015); however, the exact mechanism for this effect is unknown. Young rats maintained on a high-fat and sugar diet show reduced BDNF levels, hippocampal growth, and subsequent performance in spatial memory tests, after only one month of dietary treatment (Molteni et al. 2002), with some studies suggesting that an even shorter dietary exposure (days) to such diets may have long-term implications for cognitive function, due to inflammatory responses within the brain (Spencer et al. 2017). Choline, a B-complex vitamin with an amino acid like structure, is an essential nutrient and is particularly important during early development for effective

neural growth (Zeisel 2006) and arguably adult learning and memory (Meck and Williams 2003). Prenatal dietary supply of choline chloride to rats through maternal diet has been shown to increase subsequent spatial memory performance (Meck et al. 1988), and the mechanism is thought to involve changes in DNA methylation within stem cells controlling the proliferation of neural tissue (Zeisel 2006). However, the biological relevance is unclear, given choline intake may rarely be limited in the wild.

In birds, there has been specific interest in susceptibility of the hippocampus and spatial memory tasks to dietary restriction in food caching birds and there is considerable evidence that physiological stress affects hippocampal development, as well as learning and memory (Buchanan et al. 2013). Dietary stress during early development affects hippocampal growth/volume and spatial memory in Western scrub jays (*Aphelocoma californica*) (Pravosudov et al. 2005), whilst in the chicken chronic food stress reduces neurogenesis, but not hippocampal volume (Robertson et al. 2017). In songbirds, studies of the effects of early diet on spatial memory appear to show that early life diet can both enhance and hamper performance in spatial memory tasks (Brust et al. 2014; Farrell et al. 2015; Kriengwatana et al. 2015). For example, zebra finches subject to dietary restriction in early life show impaired exploratory behaviour only when exhibiting compensatory growth (Krause and Naguib 2011). This suggests that it may be vital to determine both the ecologically relevant dietary stressor and the behaviourally relevant task to determine whether early life diet is relevant for long-term fitness.

Experimental manipulations of micronutrient availability during early development in birds suggest there may be functional links between early life diet and the expression of neophobia, boldness and consequent survival (Arnold et al. 2007; Noguera et al. 2015; Richardson et al. 2019). There is some indication that taurine supply, an essential amino acid that varies with the invertebrate content of nestling diet, may affect the ability to remember the location of food sources (Arnold et al. 2007). However, for many of these studies the responses are sex-specific and both the direction of impact and the window of dietary sensitivity are variable, making it difficult to reach any general conclusions. Although not explicitly focused on early development, a recent relevant meta-analysis assessed the impact of compromised nutrition on behaviour and concluded that experimental reductions in nutritional conditions lead to a substantial increase in risk taking behaviours, across wide taxonomic groups (Moran et al. 2021). Despite high heterogeneity in the reported effect sizes across studies, stronger effects of nutrition on behaviour were found when experimental nutritional interventions were imposed in early life stages, or prolonged across life stages (Moran et al. 2021), suggesting early windows of behavioural programming do exist across species. Such behavioural adjustments are seen as adaptive, from the perspective of maximising the chance of survival during nutritional shortages.

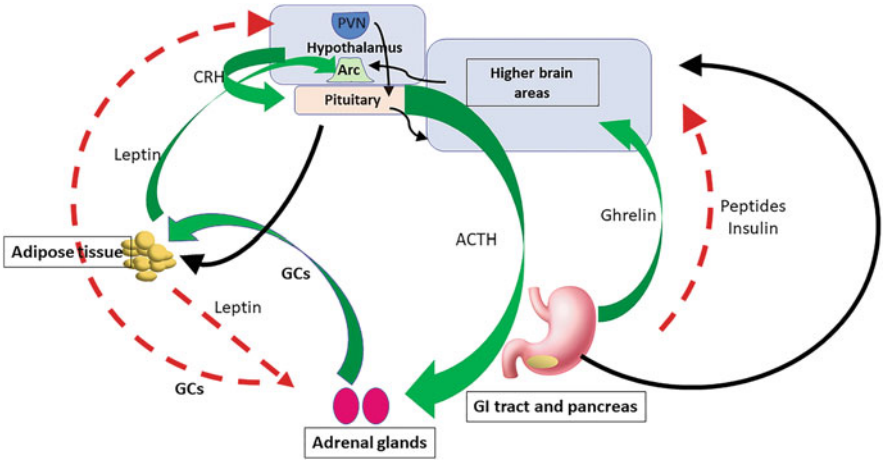

Fig. 6.2 In vertebrates, the hypothalamic-adipose axis regulates energy storage and nutritional status and embeds into the hypothalamic-pituitary (HPA) axis, which regulates energy release during basal and stressful conditions. The hypothalamus contains a number of nuclei that develop to regulate feeding behaviour, including the arcuate nucleus of the hypothalamus (Arc), which integrates peripheral information on body condition, balancing energy reserves with dietary intake. Arc is largely conserved across vertebrates in terms of its structure and neuropeptide expression. The paraventricular (PVN) nucleus is largely regarded as a satiety centre. Neuronal signals from the PVN stimulate the pituitary and regulate energy expenditure, which feeds back through the autonomic nervous system (black arrows) to adipose tissue. The HPA axis controls the response to environmental perturbations, stimulating the adrenal cortex to produce glucocorticoid (GC) hormones (e.g., cortisol, corticosterone), in response to adrenocorticotropic hormone (ACTH). GCs stimulate the release of energy from adipose tissue. Leptin production from the peripheral adipocytes reduces food intake (anorexigenic) and under acute stress, leptin attenuates the stress response. GCs also generate negative feedback effects on the hypothalamus. Receptors in Arc stimulate release of appetite-regulating neuropeptides in response to leptin, although neuropeptide function differs between vertebrate groups. Under nutritional restriction the gastric tissues release a range of peptides including ghrelin which increases feeding behaviour (orexigenic). These peptidergic hormones travel in the bloodstream to activate various targets within the CNS. The gastro-intestinal tract contains mechanoreceptors and chemoreceptors which feed signal back to the higher brain areas through the autonomic nervous system to regulate food intake. Green lines are stimulatory and red dotted lines are inhibitory. Ontogenetic development of these complex networks offers a target for developmental programming

6.2.3 Effects of Developmental Diet on Adult Physiology

6.2.3.1 Ontogeny of Control of Food Intake

The potential for diet to cause longer-term metabolic programming surely depends on the physiological responses to hunger and satiety and how these physiological responses develop. The ontogeny and neuropeptide mechanisms are best quantified in rodents (Dallman et al. 1993), with much less understanding in non-model organisms (Crespi et al. 2013; Boswell and Dunn 2017). Food intake is controlled

by the integration of both central and peripheral mechanisms generated by the gut, liver and brain (Tachibana and Tsutsui 2016). Neuroanatomical localisation of the neural centres controlling hunger are broadly conserved in vertebrates, with fundamental differences in the neuropeptides used (Crespi and Unkefer 2014; Tachibana and Tsutsui 2016), but may form the basis for developmental programming (Fig. 6.2). In early life, vertebrate food intake is controlled by internal drive to feed, which is unresponsive to external conditions and has evolved to maximise growth rates and survival chances (Crespi and Unkefer 2014). There is then a developmental switch in control of both hunger and metabolism, as hypothalamic neurons reorganise and become sensitive to signals from the gut and the body's periphery (Dobbing and Sands 1979; Grove et al. 2003; Tachibana and Tsutsui 2016). Interestingly, the response to external stressors also changes around this time. During early vertebrate life stages, the hypothalamic-pituitary-adrenal (HPA) axis is hyporesponsive. However, maturation of hypothalamic sensitivity to hunger and appetite signals coincides with the maturation of the HPA axis stress response, which then plays a crucial role in determining the future organismal responses to nutritional content and availability (Crespi and Unkefer 2014) (Fig. 6.2). Any proximate mechanisms for HPA axis programming by early life diet may therefore rely on specific sensitive windows relating to neural development. Specifically, this would be when the HPA axis through the hypothalamus embeds into the developing melanocortin system, neurons that express a range of neuropeptides directly or indirectly involved in the regulation of food intake, e.g., neuropeptide Y (NPY), agouti-related peptide (AGRP) and proopiomelanocortin (POMC) (Schwartz et al. 2000; Grove et al. 2005; Breton 2013; Tachibana and Tsutsui 2016). These complex neurophysiological networks then set the basis for controlling adult appetite, foraging and food intake, in association with the circadian rhythms in baseline glucocorticoid concentrations (Sapolsky et al. 2000). In mammals, the secretion of adipocyte-derived leptin is directly affected by the nutritional environment (Fig. 6.2), whilst this hormone plays an important role in determining projections from Arc to other hypothalamus regions (Simerly 2008; Friedman 2009; Breton 2013). Therefore, it seems possible that at least for mammals, leptin may play a crucial role in mediating the development of hypothalamic control over food intake and the subsequent hypothalamic responses to food supply (Simerly 2008; Bale et al. 2010; Dietrich and Horvath 2013). However, neuronal circuits within Arc in adult rats show substantial plasticity, suggesting that intake may be more likely to respond to immediate conditions and perhaps reducing the potential for long-term programming by early diet (Dietrich and Horvath 2013).

Comparatively, the ontogeny of control of food intake is understood to variable degrees in non-model organisms. It is not well understood in fish (Hou and Fuiman 2020) or altricial birds (Boswell and Dunn 2015, 2017). The precocial chicken (*Gallus gallus*) is the best-studied avian system, with 9-day-old chicks somewhat responsive to leptin (Cassy et al. 2004), but the ontogeny of food control is not well quantified even in precocial birds. In some mammalian species that are precocial but have longer gestation periods (non-human primates and sheep), hypothalamic regulation of food intake develops before birth (Crespi and Unkefer 2014).

Environmental factors play an important part in programming food intake in later life in anurans (Hu et al. 2008) birds (Kitaysky et al. 2006) and mammals (Meaney 2001; Shin et al. 2012). In anurans, the intriguing reformation of the gut and radical dietary change which occurs across metamorphosis has driven extensive research into the control of food intake (Crespi and Unkefer 2014). Like other vertebrates, in anurans, the anorexigenic controls that the hypothalamus exerts are absent in the tadpole stage and develop at metamorphosis and coincidentally with the onset of leptin production (Bender et al. 2018). In addition, there is interesting comparative evidence that selection during these larval feeding stages has fundamental implications for adult morphology (Bardua et al. 2021).

Identifying the mechanisms affecting developmental change and sensitive windows is therefore enormously challenging. In birds, several studies have shown the involvement of corticosterone and testosterone in controlling begging behaviour and food intake, in taxonomically diverse groups such as seabirds and songbirds (Kitaysky et al. 2001b; Goodship and Buchanan 2006). Identification of mammalian leptin as a crucial hormone regulating satiety (Zhang et al. 1994) was followed by its identification in anurans, fish and eventually, after a 20-year search, in birds (Friedman-Einat and Eyal Seroussi 2019). However, although leptin clearly plays a central role in regulating food intake in adult mammals, its role in non-mammalian vertebrates is much less clear (Boswell and Dunn 2015; Friedman-Einat and Eyal Seroussi 2019). Similarly, whilst ghrelin plays an essential role in mammals communicating nutritional state to the brain, driving food consumption and food hoarding, in birds the response can be quite variable (Boswell and Dunn 2015; Tachibana and Tsutsui 2016). Ghrelin levels, however, are associated with body fat stores and migratory restlessness in garden warblers (*Sylvia borin*) (Goymann et al. 2017). These fundamental differences between how food intake is regulated between adult birds and mammals have been suggested to have their evolutionary origins in the differences of metabolic demands and perhaps the high metabolic demands of flight (Boswell and Dunn 2015).

6.2.3.2 Physiological Consequences of Intake Rates

The adaptive setting of nutritional intake is important as either dietary restriction or caloric excess in rodent maternal diets leads to an increased risk of adiposity, neural inflammation, altered HPA function, metabolism and hyperphagia in their adult offspring (Schenk et al. 2008; Lumeng and Saltiel 2011) (Fig. 6.3). Central to the physiological mechanisms mediating these effects in vertebrates is thought to be the early programming of the sensitivity of the HPA axis by early life experiences (Levine 2005; Meaney et al. 2007; Crespi et al. 2013). The HPA axis (HP-interrenal axis in amphibians and fish) operates at a 'baseline level', responding to environmental challenges through the release of corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary, stimulating the production of glucocorticoids by the adrenal glands (Sapolsky et al. 2000). This results in complex physiological interplay resulting in

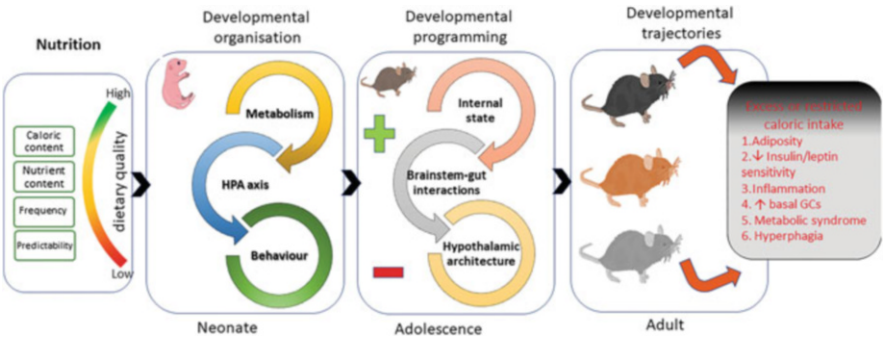

Fig. 6.3 The drivers for food regulation, metabolism and the impact of early life experience on adult physiology and behaviour are best understood in the rodent model. Similar effects have been detected when manipulating either maternal or early neonate diet. Nutritional supply and content act to determine dietary quality, which in early life impacts to organise metabolic pathways and the physiological response to stress. The impact of nutrition on development starts in early development when the initial state, determined by the initial food supply, affects communication between the brainstem and gut, including the production of peripheral hormones. This communication starts to determine hypothalamic development, which in turn takes over as the integrator of gut-brain signals and the primary regulator of food intake around weaning. Stress responsiveness also develops with age, allowing for pups to maximise intake during the neonatal period. After weaning, the stress response plays an adaptive role in mediating between risk and foraging to allow independent offspring to balance energy requirements with risky behaviours. The hypothalamic architecture will also determine appetite and metabolism, which has long-term implications for adult energetic demands. The period of transition from food intake regulated primarily by the gut and brainstem to intake regulated by hypothalamic nuclei may represent a developmental window during which metabolic programming can occur

increased cerebral blood flow, appetite suppression, the mobilisation of stored energy reserves through gluconeogenesis, raising blood sugar levels (Sapolsky et al. 2000). Whilst, short-term responses to environmental challenges tend to result in increased energy mobilisation, the strength and duration depend on prior experience, with the repeated demonstration of the impact of early life conditions on HPA axis sensitivity (Levine 1967; Matthews 2002; Meaney et al. 2007). Rats exposed to prenatal stress (maternal stress, which is not always dietary stress) demonstrate a hyper-responsive HPA axis with attenuated shutdown, resulting in chronically elevated glucocorticoid levels (Matthews 2002; Levine 2005). Short-term food restriction results in activation of the HPA axis in birds (Lynn et al. 2003) and mammals (Diaz-Munoz et al. 2000). However, some restrictions are more predictable (e.g., diurnal or seasonal changes in food availability), generating periods of adaptive adjustment in foraging, mass and HPA function (Wingfield et al. 1998). In contrast, the adaptive regulation hypothesis suggests that animals cope with unpredictable food availability, by decreasing their energetic demands and protecting stored energy reserves (Witter et al. 1995; Fauchald et al. 2004), as well as attenuating their HPA response. However, unpredictable food supplies can lead to increased glucocorticoid production, or alterations to HPA axis function, in accordance with the chronic stress hypothesis (Clinchy et al. 2004; Fokidis et al. 2012).

These competing theories are relevant for understanding the potential for adaptive HPA programming for adult environmental conditions. In nestling altricial birds, it seems that prolonged dietary restriction during early development can result in chronic elevations of baseline glucocorticoid production in later life (Kitaysky et al. 2001a; Kriengwatana et al. 2014) (but not always, see Spencer et al. 2003). It seems therefore that whilst early life conditions do have the potential for long-term adaptive programming for adverse conditions (Spencer et al. 2009), not all changes to dietary intake cause long-term changes in HPA axis function.

The effects of early nutritional conditions on adult metabolism have attracted enormous attention in terms of attempts to explain metabolic syndromes in later life, as well as to identify risk factors for a range of human health conditions (McMillen and Robinson 2005). Proposed mechanisms for the well-documented metabolic programming from rodent studies (Fig. 6.3) include alterations to HPA axis sensitivity, insulin regulation and resistance, kidney, cardiac and vascular development and function, as well as appetite regulation, with epigenetic mechanisms attracting increasing interest (McMillen and Robinson 2005). However, comparative evidence for the long-term effects of early life diet on adult metabolism is mixed. In mammals, although caloric restriction reduces metabolic rate during restriction and impacts body mass and composition, the long-term impact on metabolism is highly variable, depending on individual mass and the severity and duration of nutritional restrictions (Heilbronn and Ravussin 2003). Whether a nutritional challenge impacts adult metabolism may depend on the developmental processes taking part in different tissues during this critical window (Hales and Barker 1992). In fish, early nutrition affects growth, as well as nutrient uptake and metabolism (Hou and Fuiman 2020) and the duration of the larval and embryonic periods, which have a high potential for metabolic plasticity and programming, compared to the juvenile phase (Hou and Fuiman 2020). However, no studies have experimentally demonstrated the long-term impact of early life diet on adult fish metabolism. An interesting study on the impacts of predation on dietary intake in grasshoppers concluded that the increased metabolic demands under high predation risk drive changes in dietary preferences, with consequences for nutrient turnover within the environment (Hawlena and Schmitz 2010). In altricial songbirds, food restriction in the nestling phase results in increased metabolic rates in adult female (but not male) song sparrows (Schmidt et al. 2012) and zebra finches (Careau et al. 2014). Caloric restriction also reduces inter-individual variation in individual behaviour and physiology by canalising the developmental process to produce less variable phenotypes (Careau et al. 2014). However, zebra finches raised in larger broods have increased standard metabolic rate independent of mass as adults (Verhulst et al. 2006), perhaps suggesting that other aspects (e.g., growth rates, thermal environment, competition) of developmental conditions play an important role in determining adult metabolism, in addition to caloric intake. Dietary protein during nestling development has also been shown to affect growth rates and nestling resting metabolic rate (RMR), with low dietary protein resulting in elevated nestling RMR (Criscuolo et al. 2008). However, in this study adult RMR was only affected by dietary protein levels if they experienced a dietary treatment which required catch up compensatory growth (Criscuolo et al.

2008), suggesting the process of compensating for a bad start in life may contribute to adult metabolism. Together, these avian studies suggest that compensatory growth may be particularly important in determining adult metabolism (Verhulst et al. 2006; Criscuolo et al. 2008), but both mechanisms and consequences are unclear.

6.2.4 *Nutritional Balance, Diet Composition, and Optimising Development*

The relationship between diet and fitness relies on the concept of nutrient balance meeting current demands and the interaction of the animal with its environment (Simpson and Raubenheimer 2012). The integrated framework of nutritional geometry was first developed in the early 1990s to explain the how and why nutrition impacts development and the adult state (Simpson and Raubenheimer 2012). It considers the nutritional regulatory systems which are most relevant for fitness-related traits such as macronutrients, e.g. proteins, carbohydrates and lipids or essential minerals such as calcium or phosphorus (Maklakov et al. 2008; South et al. 2011). This framework has been useful in identifying the likely drivers that explain outcomes which may optimise health and fitness (Hunt et al. 2004; Simpson et al. 2015). The framework addresses the nutritional constraints of optimising intake when food comes in packaged units comprising relative proportions of required macronutrient components, such as protein and carbohydrate. Therefore, optimising dietary intake depends on their relative proportions and the amount eaten across development (Fig. 6.4). Instead of maximising the intake of multiple nutrients, individuals discriminate to optimise the ratio which best supports development (Simpson and Raubenheimer 2012). The nutritional framework for an animal's optimal dietary intake therefore has to be multidimensional. Whilst complex, the last 30 years have seen considerable gains in identifying the nature of these dimensions (Harrison et al. 2014). The nutritional geometry framework has repeatedly identified macronutrients such as proteins, lipids and carbohydrates as powerful drivers controlling developmental processes (Raubenheimer 1993; Raubenheimer and Simpson 1993). The field of nutritional geometry developed from a complementary conceptual framework of ecological stoichiometry (the study of energy balances and multiple chemical elements in living systems (Elser 2006). This approach generally models the stoichiometric flow of individual chemical elements through biological systems and their reorganisation (Sterner and Elser 2002). The importance of macronutrients in driving development is also supported by the approach of ecological stoichiometry, which confirms that nitrogen, carbon and phosphorus are pivotal for determining fundamental ecological processes (Anderson and Pond 2000; Elser et al. 2000). These two approaches confirm the essential importance of balanced nutritional intake for optimising development, longevity and fitness.

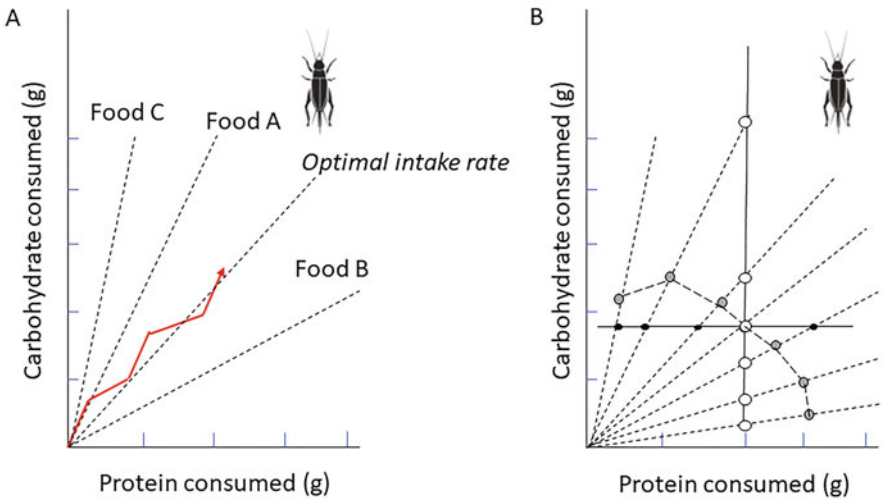

Fig. 6.4 (**a**) The nutrient space of a hypothetical animal consuming nutritional components, here protein and carbohydrate. In order to balance nutritional intake, animals regulate the relative intake of key nutritional components, such as protein and carbohydrate. Here, the optimal intake rate for this cricket is 1 unit of carbohydrate for each unit of protein. Whilst some foods may offer the optimum composition for balanced intake, available food may not have a balanced composition and have, for example, a higher ratio of carbohydrate: protein (Food A) or a higher ratio of protein: carbohydrate (Food B) than is optimal. Animals optimise their intake by switching between the available food options. When offered a choice of Food A and B, the animal will seek to balance intake by switching (red line). But if the animal has only a choice of Food A or Food C, then the animal cannot optimise intake and must utilise 'rules of compromise' to balance the over or under consumption of key nutritional components. It is important to recognise that the nutritional landscape is multidimensional and varies not only in protein:carbohydrate but also in many nutritional components. (**b**) The rules of compromise used by animals can be deduced by keeping discrete groups of animals on different food sources (dotted lines) of the different nutritional compositions. The resulting intake rates show patterns such as the vertical line (open circles)—maximise protein intake, or the horizontal line (filled circles)—maximise carbohydrate intake. Alternatively, (shaded circles) show an asymmetrical response that differs according to the level of surplus consumption. Such approaches are useful for understanding the nutritional drivers for optimal development and, therefore, related nutritional costs of compromise. Adapted with permission from Simpson and Raubenheimer (2012)

In insects, a raft of no choice experiments has demonstrated that diet composition optimises the development of particular traits over others and which nutritional components are important (e.g., Simpson et al. 2004; Lee et al. 2008; Fanson and Taylor 2012; Lee et al. 2013; Sentinella et al. 2013). However, the rates of consumption of the different nutritional components drive not only physiological processes and development, but also future dietary choice (Lee et al. 2012). Allowing animals to actively choose a particular diet has allowed for experimental demonstration of diet optimisation over time in a context dependent manner (e.g., Lee et al. 2008; Fanson and Taylor 2012), as well as demonstration of selection on

fitness parameters, such as lifetime egg production (Lee et al. 2008). Caterpillars are vulnerable to poor body condition from either low-protein or carbohydrate intake, before metamorphosis. Early instar caterpillars (*Spodoptera litura*) raised on low-protein diets adaptively increase their protein intake when available, increasing their chances of successful metamorphosis and survival (Lee et al. 2012). Such adaptive changes in dietary intake may be sex specific. For example, in *D. melanogaster*, longevity is reduced by increased protein intake, a relationship repeatedly demonstrated across broad taxonomic groups (Simpson et al. 2017). Indeed, bacterial infection causes a shift to a more carbohydrate diet in *D. melanogaster,* an adaptive dietary shift which appears to increase immunity and survival (Ponton et al. 2020). In choice experiments, adult male *D. melanogaster* opt for the same protein to carbohydrate ratio as experienced in early development, but no effect of early developmental diet is seen on female dietary choice (Davies et al. 2018). This sex-dependent programming of dietary intake may be due to differences in the energy demands of the sexes and trade-offs with longevity (Davies et al. 2018).

In any discussion of the impact of early life diet on adult phenotype, it would be remiss not to mention the importance of the microbiome for development and fitness (Suzuki 2017). The bacterial community of the gut determines host metabolism, digestion and nutrient uptake in interaction with the host immune system, but equally is affected by the dietary choices made by organisms (Tremaroli and Backhed 2012; Lindsay et al. 2019). Thus the relationship between host microbiota and development is a labile relationship which may change to enable optimisation of nutrient uptake or constrain developmental processes. The rapid development of low-cost sequencing techniques has driven exciting new research in this field to quantify these complex interactions, and this is a rapidly changing and exciting field of research. For example, alterations in the mouse microbiome in infancy can interact with early life nutrition to induce metabolic changes that promote long-lasting obesity (Cox et al. 2014). Quantifying the interactions between diet, host microbial community, metabolism and growth seems likely to reveal some fundamental insights into the factors determining plasticity in development (Lindsay et al. 2019).

6.2.4.1 Micronutrients as Limitations

Aside from optimising the broad-scale ratio of macronutritional components, the availability of various essential micronutrients can have long-term effects on growth and development, as well as long-term fitness (Harrison et al. 2011). But whilst numerous micronutrients (e.g., magnesium, phosphorus, zinc) are essential for growth, development and reproduction, whether these have any biological relevance depends on the likelihood of dietary restriction. Iron is the most commonly restricted micronutrient in human populations and essential for normal neural development during early life, as deficiency can lead to compromised neural growth and cognitive function. In human populations approximately 30-50% of pregnancies are thought to

be affected (Rao and Georgieff 2007), resulting in routine dietary supplementation during early pregnancy to protect foetal development. Identification of the sensitive window for neural development from iron depletion is now being addressed in mammals using knockout models, with reversible repletion of iron to identify the period of vulnerability (Fretham et al. 2012). Such techniques will be invaluable for addressing vulnerability in other taxonomic groups. Aside from purely addressing limitations, micronutrient intake must be balanced, and an interesting example of the effects of exceeding optimal intake levels is the impact of excess sodium intake due to road run-offs on butterflies. Ecologically relevant increases in sodium levels in milkweed plants affected the growth and development of both monarch (*Danaus plexippus*) and cabbage white butterflies (*Pieris rapae*) (Snell-Rood et al. 2014). Consistently, increased sodium intake led to increased muscle mass in males across these two species and increased neural development in female butterflies (Snell-Rood et al. 2014), suggesting that this may lead to differences in behaviour and ecology.

Antioxidants have received substantial interest in recent years, in terms of their potential to limit oxidative stress and mediate fundamental life-history trade-offs (Catoni et al. 2008; Monaghan et al. 2009). Whilst carotenoids have attracted most attention and been shown to affect adult sexual traits and immune function (Blount et al. 2003a, b), a variety of other nutritionally limited antioxidants are potentially important, including Vitamin C, Vitamin E, anthocyanins and polyphenolic antioxidants (Catoni et al. 2008). In terms of their relevance to development, their main benefit may lie in offsetting any oxidative stress costs of rapid growth. Vitamins C and E have been reported to improve growth rates in young mammals, fish and birds (e.g., Cromwell et al. 1970; Sealey and Gatlin 2002; de Ayala et al. 2006; Catoni et al. 2008), but whether the long-term effects of oxidative stress are mediated is mostly unknown. In zebra finches, a short period of food restriction in early life affects adult circulating levels of antioxidants, suggesting that the uptake or transportability of dietary challenged birds is somehow compromised during development (Blount et al. 2003a), but the mechanism for this effect is unclear. As mentioned above, one possibility is that nutritional restriction in early life causes long term changes to the gut microbiota, which alter digestive function and absorption of key nutrients. In humans, there are clear links between early life nutrition and the establishment of the subsequent microbiota, with consequences for health in later life (Forgie et al. 2020; Ratsika et al. 2021). The establishment of particular microbial communities is dependent on diet, determines the capacity to metabolize macronutrients and it seems likely that this plays an important long term role in determining uptake of a range of nutrients, such as ellagitannins which are metabolized to urolithins, both of which have antioxidant potential (Hullar and Fu 2014). Growth rates are implicated as mediators of oxidative stress, as faster growing zebra finches have reduced antioxidant capacity after a period of compensatory growth (Alonso-Alvarez et al. 2007). Consistent with the hypothesis that dietary antioxidants play an important role in mediating the trade-offs during growth and development, in both red winged blackbirds *(Agelaius phoeniceus)* (Hall et al. 2010) and European seabass (*Dicentrarchus labrax)* (Costantini et al. 2018) increases in

antioxidant availability allow compensatory growth. However, antioxidant supplementation experiments often do not demonstrate any impact on longevity, in part because dietary supplementation sometimes results in a shift in the production of endogenous antioxidants in laboratory studies (Selman et al. 2006; Monaghan et al. 2009). The relevance of dietary antioxidants in mediating long-term changes to phenotype and fitness trade-offs in wild animals therefore remains unclear and an active area of research (Catoni et al. 2008).

6.3 Developmental Plasticity: Phenotypic Consequences of Nutritional Vulnerability

Environmental factors strongly influence how animals procure, compose, and provide the nutrition needed for offspring development (Monaghan 2008; Boggs 2009; Wilkin et al. 2009; Georgieff et al. 2015; Howells et al. 2017). In particular, climate and habitat variation can produce extreme temporal (e.g., prey densities for predators) or spatial (e.g., forage supply and composition for herbivores) differences in the food quality and quantity available to offspring (Madsen and Shine 2000; Coudrain et al. 2016; Pollock et al. 2017). Additionally, offspring can also experience variable early life nutrition due to parental food provisioning biases or kin competition—common behaviours in nature (Drent and Daan 1980; Kacelnik et al. 1995; Lessells 2002). For example, adult male albatross (*Diomedea exulans*) provide more food to male than female chicks, contributing to sex-specific life-history differences (Weimerskirch et al. 2000). Similarly, first, born killifish (*Nothobranchius rachovii*) can better monopolise parental food resources better than their subsequent siblings to create considerable differences in early life nutritional experiences largely invariant to the external environment (Schrader and Travis 2012).

Thus, the diet of the young, influenced by environmental or parental circumstances, can result in episodes of compromised nutrition, suboptimal for normal development. Exposures to under- or overnutrition- (i.e., nutritional stressors) are notable for their often extraordinary capacity to induce diverse, amplified and often life-long phenotypic consequences (Langley-Evans 2009; Beldade et al. 2011; Gluckman et al. 2011; Moczek et al. 2011; Nijhout 2015). The magnitude and duration of 'non-optimal' nutrition in early development are both important for determining the diverse phenotypic and fitness consequences across ontogeny (Regan et al. 2020). However, the specific timing of nutritional stressors within early development is also crucial for determining impact, which is especially important for understanding variation in their mechanistic and evolutionary consequences (Fawcett and Frankenhuis 2015; English and Barreaux 2020) As early life is replete with molecular and cellular processes responsible for the unprecedented rate of developmental growth and change, organisms are highly responsive and susceptible to environmental stimuli (West-Eberhard 2003). Indeed, exposures to nutritional variation can induce a multitude of departures from optimal developmental

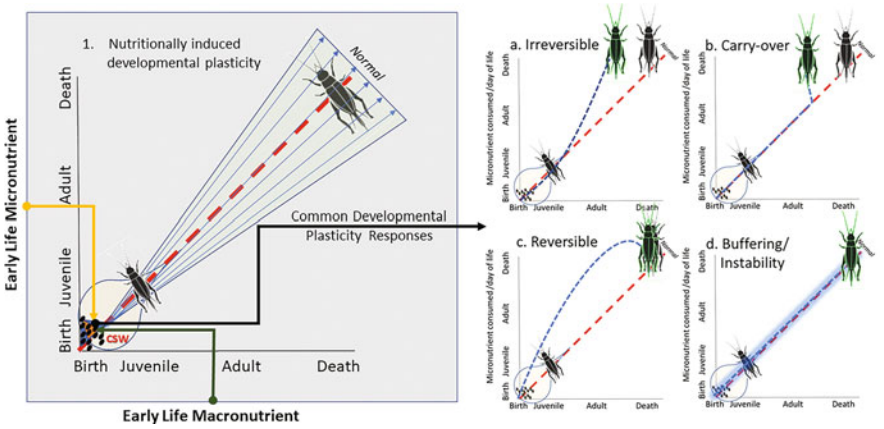

Fig. 6.5 This schematic depicts how early life nutrition, one of the most potent and complex environmental stimuli, can induce complex variation in developmental plasticity in animals. This is because different regimes of early life macro and micronutrients can act on critical and sensitive developmental windows (CSW) to induce complex phenotypic consequences (i.e., abnormal phenotypic trajectories as represented by arrows) across ontogeny. Although nutritional stressors can produce diverse developmental consequences, studies typically report several common phenotypic response outcomes across including (**a**) *irreversible developmental plasticity* that comprises strong and long-lasting phenotypic consequences; (**b**) *carry-over effects* that see phenotypic consequences of early life nutrition expressed at later periods within or between life stages; (**c**) *reversible developmental plasticity* where the effects of nutrition act on developmental windows that induce initially strong, but reversible phenotypic plasticity and (**d**) *phenotypic buffering and instability* type responses which are when nutritional stressors are attenuated by developmental systems that have some degree of buffering capacity (i.e., reduced sensitivity) or instead produce developmental instability, observed as inflated phenotypic variance, consistent with fluctuating asymmetry

trajectories that mediate how individuals express life-history traits, succumb to non-communicable diseases and ultimately explain prolific differences in their fitness (Hu et al. 2008; Monaghan 2008; Faulk and Dolinoy 2011; Moczek et al. 2011; Lucassen et al. 2013; Langley-Evans 2015; English and Barreaux 2020). This section describes how interactions between early life nutrition and developmental timing can induce multiple modes of developmental plasticity, that range from heightened irreversible and reversible phenotypic consequences to the expression of more subtle forms of plasticity buffering normal phenotypic trajectories (Fig. 6.5).

6.3.1 The Basic Mechanics of Nutritional Influences on Developmental Plasticity

Why does early diet profoundly influence the attributes of later life traits, whilst adult diet does not? In part, this is because early life nutrition is considered one of the most potent and complex environmental stimuli to induce developmental plasticity (Rice

and Barone 2000; Georgieff et al. 2015; Mueller 2018). As such, nutritional experiences in early life can produce particularly strong and potentially permanent phenotypic consequences (Nowicki et al. 2002; Schulz 2010; Fawcett and Frankenhuis 2015; Frankenhuis and Walasek 2020). In developmental biology, *critical* and *sensitive* windows are terms used to describe transient periods in which environmental factors induce stronger or long-lasting phenotypic responses at key developmental stages (Rice and Barone 2000; Georgieff et al. 2015; Mueller 2018). Additionally, because of functional differences, critical and sensitive windows can confer different modes of plasticity that see the induction of irreversible or reversible phenotypic consequences expressed across one or more life stages (Rice and Barone 2000; Piersma and Drent 2003). However, designating critical or sensitive periods in early life ultimately hinges on the interplay between attributes of the nutritional experience and how an individual's cellular and molecular processes regulate tissue and organ-specific developmental trajectories (Michel and Tyler 2005; Thomas and Johnson 2008; Panchanathan and Frankenhuis 2016). For example, moderate levels of caloric restriction versus reduced methyl donors or micronutrients in early development are associated with major differences in how molecular-based critical windows (i.e., epigenetic mechanisms) trigger developmental plasticity and later life consequences (Ramos-Lopez et al. 2019).

The nutritional environment, either by way of perturbations to nutrient signalling or to the direct supply of energy and nutrients, provides cues that affect critical or sensitive periods in cellular proliferation, migration and differentiation needed for normal development (Rice and Barone 2000; Fretham et al. 2012). Furthermore, critical and sensitive windows are often underpinned by nutritional modification of epigenetic factors, either inherited or directly induced, which provides an important molecular basis for phenotypic plasticity to arise in early development within and across generations (Langley-Evans 2009; Faulk and Dolinoy 2011). Indeed the perinatal epigenome, established during cellular differentiation, is extremely susceptible to variation in the nutritional environment (Morisson et al. 2017).

At least mechanistically, because critical or sensitive periods in cellular or molecular processes often diminish after early development, so does the capacity for the nutritional variation to induce heightened and potentially long-lasting plasticity in later life (Clinchy et al. 2004; McGowan et al. 2008; Monaghan 2008; Faulk and Dolinoy 2011; Georgieff et al. 2015). A simple demonstration of this principle is that in *D. melanogaster*, the larval diet governs adult trait sizes that are otherwise unresponsive to the adult diet (Poças et al. 2020). It is important to recognise that within the literature, some observations of nutritionally evoked developmental plasticity are commonly drawn from nutritional extremes and pathological settings (e.g., famine), where the ecological or evolutionary relevance is less clear. Here, it is logical to expect that the capacity to observe discreet phenotypic outcomes (e.g., reversible or permanent plasticity) is reinforced by a subset of more extreme under- or over-nutrition scenarios (Lucas 1991; Langley-Evans 2009; Simpson and Raubenheimer 2012). However, similar to all non-lethal environmental mediators, the degree of induced developmental plasticity, even to the same stimuli, can result in considerable heterogeneity in reaction norms of plasticity among and within

individuals (Van Buskirk and Steiner 2009). Also unclear is the ecological relevance of temporal aspects of onset. For example, do sudden changes in food availability provide a greater challenge for developing organisms than a gradual decline?

Indeed, the ability of nutrition to affect sensitive or critical developmental periods, or in the absence of such windows, to promote plasticity is highly variable among species, individuals and even between similar traits within or among individuals during development (Panchanathan and Frankenhuis 2016). For example, repeat exposures to nutritional stressors across zebra finches early life indicate how trait-specific critical periods lead to different chronologies in developmental plasticity responses for growth, body composition and immune function (Kriengwatana et al. 2013). Ultimately, however, nutritional effects on developmental critical or sensitive windows provide a major basis to the substantial phenotypic variation observed among individuals or cohorts, all without any genetic underpinning.

6.3.2 *Early Life Nutrition, Critical Windows, and Irreversible Developmental Plasticity*

For decades, it has been recognised that aberrant early life nutritional experiences that coincided with specific tissue or organ development periods can produce strong and long-lasting phenotypic consequences (Colombo 1982; Rice and Barone 2000; Hensch 2004). These phenotypic outcomes are consistent with how environmental processes affect critical developmental windows (Mueller 2018). In essence, a critical window reflects time-sensitive interactions among genetic, environmental, epigenetic and developmental processes that cause phenotypes to permanently deviate from normal developmental trajectories (Burggren 2020). Importantly, the onset, duration and endpoint of critical periods are regulated by developmental molecular processes that constrain further plasticity to subsequent dietary variation (Dehorter and Del Pino 2020). For example, it is understood that the onset and length of critical windows that influence neural plasticity in response to nutritional stimuli can be governed by the maturation of GABAergic interneurons (Neuringer et al. 1986; Marín 2016).

However, critical periods also possess many other attributes that ultimately affect how environmental interactions invoke phenotypic consequences arising in development (Burggren 2020). For instance, critical periods vary in timing of onset, duration, number per trait, and sensitivity across organs and environmental stimuli (Rice and Barone 2000; Mueller 2018; Burggren 2020). Nevertheless, critical windows allow nutritional stimuli to elicit multiple modes of irreversible phenotypic plasticity (Bornstein 1989; Lucas 1991; Gluckman and Hanson 2004; Langley-Evans 2009).

Interactions between early life nutrition and critical windows can cause individuals to express either ‘immediate’ (Fig. 6.5b) or ‘deferred’ (Fig. 6.5c) modes of irreversible phenotypic plasticity (Lucas 1991; Rice and Barone 2000; Pechenik

2006; McGowan et al. 2008; Li et al. 2010; Moore and Martin 2019). For example, some nutritional programming consequences create interactions between early life nutrition and tissue or organ-specific critical windows to result in immediate and permanent phenotypic modification (Moczek et al. 2011; Lee et al. 2012; Nijhout 2015). Such consequences are especially common in species with direct development (Allen and Marshall 2013; Burggren 2020). For instance, optimal neural differentiation requires a disproportionate amount of energy delivered to the brain and a tightly scheduled supply of essential nutrients (see Sect. 6.2.4) (Isler and Van Schaik 2006; Georgieff et al. 2015). Hence, periods of whole organism undernutrition that coincide with critical periods of neural differentiation can result in immediate and irreversible life-long cognitive and behavioural consequences for many species (Bateson and Horn 1994; Fisher et al. 2002).

Similarly, the broad-scale evidence across animals that overnutrition acting on critical periods in early development accelerates early somatic growth and results in larger body size at maturity is another good example of immediate onset and irreversible developmental plasticity (Deeming 2004; Monaghan 2008; Ferreira and Milán 2015; Koyama and Mirth 2018). Indeed, such developmental responses can be pronounced in governing an individual's growth rate. For instance, individual growth trajectories in water pythons (*Liasis fuscus*) show more than tenfold variation and are more determined by prey availability in early life than any corresponding later life prey intake (Madsen and Shine 2000). Additionally, better early life nutrition, via faster developmental growth rates, can substantially increase female roe deer (*Capreolus capreolus*) body size and allow for greater fecundity (Douhard et al. 2014). Such studies highlight both the permanency and magnitude of early life nutritional effects on animal phenotypes.

Rather than obvious developmental effects occurring during the nutritional stress, nutritional stressors can also produce deferred irreversible phenotypic consequences when coinciding with critical developmental windows (Pechenik 2006; Moore and Martin 2019). Deferred responses, often termed carry-over or latent effects are not expressed until later periods within or between life stages (O'Connor et al. 2014). Thus, carry-over effects are predicated on a clear transitional period that segregates the environmental impact on development from the lagged effects on phenotypic or fitness consequences (Ryo et al. 2019). Intuitively, latent effects resulting from developmental nutrition are widely reported in species with complex life cycles (e.g., taxa with indirect life cycles and demonstrate metamorphosis (Pechenik et al. 1998; Pechenik 2006). Nutritional carry-over effects have been reported to have later life phenotypic consequences in insects (Fuentealba and Bauce 2012; Vantaux et al. 2016), fish (Smith and Shima 2011; Goldstein and Sponaugle 2020), frogs (Warne and Crespi 2015) and marine invertebrates (Marshall and Morgan 2011; Marshall et al. 2016). A specific example includes how early life nutrition in female honey bees regulates a polyphenism that produces different female castes (Cridge et al. 2015). Larvae provisioned with a nutrient-rich diet (i.e., royal jelly) develop into queens, whilst those fed a nutrient-poor diet (i.e., worker jelly) develop into workers. Although larvae are fed, the subsequent pupal phase is not, and thus dietary-induced

changes in phenotype are carried over to be expressed in the adult stage (Buttstedt et al. 2016).

Species with direct development can also experience nutritionally induced carry-over effects (Cooper and Kruuk 2018); studies of birds (Lindström 1999), reptiles (Madsen and Shine 2000) and mammals (Lindström 1999; Gaillard et al. 2003; Descamps et al. 2008) report this type of nutritionally mediated developmental plasticity (Cooper and Kruuk 2018). Of course, in humans, foetal nutritional programming produces very well-documented carry-over effects, exacerbated by lifestyle risk, to see the emergence of later-life health and disease issues (Hanson and Gluckman 2014). Most noticeably, poor foetal malnutrition is strongly associated with higher risk of coronary artery disease, cancer, Type II diabetes and multiple psychiatric issues in human adults (Calkins and Devaskar 2011).

6.3.3 Early Life Nutrition, Sensitive Windows, and Reversible Phenotypic Plasticity

The observation that the nutritional environment affects critical developmental periods to induce irreversible plasticity is common but not universal (Bornstein 1989; Fawcett and Frankenhuis 2015; Burggren 2020). As critical developmental windows are brief episodes nested within relatively longer developmental durations, brief exposure to aberrant environmental conditions may allow individuals to restore normal developmental trajectories without lingering phenotypic consequences when optimal conditions are restored (Burggren 2020). In the context of developmental plasticity, such responses are consistent with the effects of nutrition acting on sensitive windows that induce initially strong but reversible phenotypic plasticity (Johnson 2005; Armstrong et al. 2006; Burggren 2020). Thus, sensitive windows are expected to preside over longer developmental durations than critical periods and may provide more frequent episodes of nutritionally induced developmental plasticity (Fagiolini et al. 2009; Faulk and Dolinoy 2011; Georgieff et al. 2015).

A good general example of reversible developmental plasticity (Fig. 6.5c) is catch up or compensatory growth, a response that allows for faster than optimal growth in individuals subjected to early life nutritional restriction (Metcalfe and Monaghan 2001; Hector and Nakagawa 2012). Indeed, this response is widely observed in animal taxa, including arthropods (De Block and Stoks 2008; Hoshizaki 2019), fish (Auer et al. 2010; Al-Chokhachy et al. 2019), amphibians (Capellan and Nicieza 2007; Hector et al. 2012), reptiles (Bjorndal et al. 2003; Radder et al. 2007), birds (Bize et al. 2006; Fisher et al. 2006) and mammals (Berghänel et al. 2017; Heissenberger et al. 2020).

Similarly, transient macronutrient alteration in young altricial birds through excluding starch can alter genetic programming to reduce the expression of intestinal disaccharidases (Brzęk et al. 2009). However, this developmental impairment of enzymatic function can be completely reversed in subsequent life stages to allow for

normal digestion (Brzęk et al. 2011). Indeed, there are many notable examples of a partial or full reversal of nutritionally modified phenotypes at the molecular and cellular level in both invertebrates and vertebrates. Like all forms of plasticity, it is expected that reversible plasticity is associated with costs imposed by the need to transition the modified phenotype back within the normal range of phenotypes, especially in stochastic environments capable of inducing on-going plasticity in phenotypes (Burggren 2018, 2020). However, such costs may be trivial for species where individuals are exposed to nutritional stressors that occur over brief periods relative to their life span and thus avoid fitness costs due to phenotype-environment mismatches (Ghalambor et al. 2007; Murren et al. 2015).

6.3.4 *Evolution of Sensitive Windows of Developmental Plasticity: A Nutritional Perspective*

Both critical and sensitive windows are remarkable for allowing nutritional stressors to induce the phenotypic consequences of large magnitude and possible permanency at discreet periods during early life. These windows of hyper-plasticity likely arise as by-products of mechanisms or constraints unique to developmental processes (Dufty et al. 2002; Frankenhuis and Fraley 2017). However, critical windows can exhibit differences in sensitivity across life and occur without developmental constraints, implying an evolutionary basis (Panchanathan and Frankenhuis 2016; English and Barreaux 2020; Frankenhuis and Walasek 2020). Two general adaptive reasons are advocated for the evolution of critical windows. The first sits under the notion of predictive adaptive responses that posits individuals significantly adjust their phenotype in response to early life external environmental experiences to promote developmental trajectories that maybe strongly correlated to later life external environments and thus favoured by natural selection (West-Eberhard 2003; Gluckman et al. 2005; Ghalambor et al. 2007). Alternatively, because most environmental stressors affect the physiological state directly, they effectively modify the internal environment of developing animals. This allows the timing of critical windows to such environmental exposures with periods of hyper-plasticity allowing developmental trajectories in life-history traits to maximise fitness across future physiologically correlated life stages (Dufty et al. 2002; English et al. 2016).

Beyond these general adaptive reasons, other theories and predictive models have been recently developed to explicitly explain why natural selection would favour critical windows to be far more prevalent in early, rather than later, life (Panchanathan and Frankenhuis 2016; English and Barreaux 2020; Frankenhuis and Walasek 2020). In particular, Frankenhuis and Fraley advocate several adaptive reasons that favour the evolution of critical periods in early development (Frankenhuis and Fraley 2017). First, through increased frequency or changes in their relative strength, environmental cues are more likely to be present at some life stages than others. Consequently, if some environmental cues are more important in

early life, they could select for enhanced developmental plasticity (Frankenhuis and Walasek 2020). Second, because the information value of environmental cues changes across the lifespan, natural selection should favour critical windows of plasticity to coincide with environmental cues that provide the most reliable information concerning conditions (Stamps and Krishnan 2017). Exposure to, and hence the experience of, environmental cues in early life is unprecedented. Thus aligning the onset of critical windows in early life could maximise the information value of many types of environmental cues for informing periods of increased plasticity (Frankenhuis and Walasek 2020). Third, even if environmental cues provide similar information across ontogeny, they do not elicit similar fitness consequences, with early life stages often most vulnerable (Fawcett and Frankenhuis 2015). Thus, critical windows of phenotypic plasticity in early life stages that most benefit fitness may provide targets for selection. Fourth, across ontogeny, the costs of plasticity (e.g., trade-offs between reproduction and survival) are variable. Selection could again favour enhanced early development plasticity periods to minimise these costs (Fawcett and Frankenhuis 2015; Frankenhuis and Walasek 2020).

6.3.5 *Other Modes of Developmental Plasticity Under Nutritional Stress*

Although often a potent mediator of developmental plasticity, nutritional stress also prompts animals to use an extraordinary array of mechanisms to ameliorate their lifelong phenotypic consequences (Rion and Kawecki 2007). This is because developmental systems retain some buffering capacity (e.g., canalisation) and hence robustness to limit the effects of environmentally induced plasticity, causing substantial departures from normal phenotypic trajectories (Fig. 6.5e) (Waddington 1942; Nijhout and Davidowitz 2003; Klingenberg 2019). Indeed, most organisms utilise a combination of plasticity (i.e., a steep reaction norm) and canalisation in their phenotypic responses (i.e., flat reaction norm) to environmental variation during development (Flatt 2005; Van Buskirk and Steiner 2009). The attenuation or absence of strong plasticity to environmental variation entails functional changes to the emergence, duration and sensitivity of critical or sensitive windows in early development. Additionally, the evolutionary loss of plasticity (i.e., genetic canalisation) may result in some species simply lacking the adaptive capacity to mount phenotypic responses to environmental variation (Flatt 2005). Developmental canalisation limits the phenotype's sensitivity to environmental and genetic perturbations (Stearns and Kawecki 1994; Nijhout and Davidowitz 2003; Boonekamp et al. 2018). However, there is clear evidence that stressors still mediate some degree of developmental instability, observed as inflated phenotypic variance, consistent with fluctuating asymmetry (Hoffmann and Woods 2001).

Nutritional stressors commonly can induce these alternative forms of developmental phenotypic responses in nature. For example, starvation resistance is

common in species that exist in environments where food availability tends to unpredictably fluctuate (McCue 2010; Lee and Jang 2014). Starvation resistance is effectively a suite of selected and induced mechanisms that focus on molecular, physiological and behavioural processes that serve to buffer the consequences of nutrient and energy deprivation on survival, and if experienced in early life, also minimise disruption to normal developmental trajectories (Rion and Kawecki 2007). Metabolic flexibility, specifically the ability of individuals to reduce their basal metabolic rate, is a key starvation resistance mechanism by which species can slow their pace of life to match their energy or nutrient intake during periods of undernutrition and conserve target developmental trajectories (Auer et al. 2015). Similarly, whilst reduced body size is a common outcome of early life nutrient limitation, it is evident that many species do not reduce their brains isometrically with the rest of their body (Maurange and Lanet 2014). This neural buffering phenomenon suggests an adaptive strategy to prevent nutritionally imposed phenotypic plasticity from affecting normal CNS development (e.g., cell size and composition) essential to brain function (Maurange and Lanet 2014).

Additionally, some species are evolutionarily constrained (i.e., lack genetic variation) in their capacity to mount developmental plasticity. For instance, dietary specialists (i.e., an absence of dietary switching across ontogeny) can show remarkably limited plasticity in their digestive physiology responses to early life episodes of dietary variation. For example, nestling zebra finches, dietary seed specialists, cannot increase activity of intestinal carbohydrases (sucrase and maltase) to enhance digestion of higher carbohydrate diets (Brzęk et al. 2010). Humans unlike other mammals cannot synthesise ascorbic acid, due to a mutation causing gulonolactone oxidase deficiency, the final enzyme in the pathway leading to the production of Vitamin C, essential for building collagen and without Vitamin C supplementation in the diet humans develop disorders such as scurvy (Gilbert 2001).

Nutritionally-induced developmental instability has been inferred by measuring either fluctuating asymmetry or coefficients of phenotypic variability of one or more traits, but the evidence is inconsistent within the literature (Fig. 6.5d) (Bubliy et al. 2001; Hoffmann 2003). For example, nutritional restriction in early development has been associated or directly related with increased fluctuating asymmetry in one or more traits of birds, mammals and arthropods (Swaddle and Witter 1994; Badyaev et al. 2000; Sillanpää et al. 2010). But many studies do not report an effect of nutritional restriction on developmental instability, even though they may report a strong overall effect on developmental growth, trait size or shape (Stige et al. 2004; Hoffmann et al. 2005; Gonzalez et al. 2014). This absence of developmental instability due to nutritional stressors could arise for multiple reasons, including that such errors in development may accumulate in late ontogeny; or that mechanisms responsible for developmental buffering are sufficiently robust or non-costly to limit phenotypic noise under these stressful conditions (Milton et al. 2003; Gonzalez et al. 2014).

6.4 Ultimate Impact: Effects on Fitness and Targets for Selection

Knowledge of how variation in early life environmental conditions impact the fitness of wild animals is important for predicting the demographic consequences of environmental variation. As detailed throughout this chapter, the early life nutritional environment is known to shape an individual's phenotype profoundly. However, from an evolutionary perspective, our understanding of the ultimate causes of such phenotypic changes and associated fitness effects remains limited. This final section summarises theoretical and empirical knowledge of how variation in early life nutritional conditions impacts fitness. Advances in understanding these ultimate effects of early life nutrition are increasingly recognised for their importance to public health management of human populations and predicting how wild animals, via cohort induced demographic or evolutionary consequences, respond to later life environments (Descamps et al. 2008; Langley-Evans 2015). This section addresses the relationships between early life nutrition and longevity, fitness trade-offs, adaptive responses, and transgenerational impacts.

6.4.1 Nutritional Intake and Longevity

The impact of nutrition on longevity has been a major area of research for nearly a century, because of the discovery in the 1930s that nutritional restriction after weaning prolongs lifespan in laboratory rats (McCay et al. 1935). Since this first report, dietary restriction (i.e., a reduction of food intake without malnutrition) at adulthood has been linked to increased lifespan across a wide range of distantly related organisms, ranging from yeast to mammals (Masoro 2005; Fontana et al. 2010; Nakagawa et al. 2012). Since this life-extension effect is consistent across taxonomic groups, it is often assumed that the response to dietary restriction and its underlying mechanisms are evolutionary conserved (Templeman and Murphy 2018; Moatt et al. 2020). The mechanisms underpinning this effect are still poorly understood. However, they may involve changes to nutrient sensing, insulin regulating pathways to regulate repair, as well as oxidative damage by free radicals generated through the digestion and uptake of nutrients, impacting on cellular and organismal ageing (Sohal and Weindruch 1996). It is also worth noting that dietary manipulations which alter intake rates through temporal availability, but not absolute caloric intake can also have have positive organismal effects, improving longevity, potentially through impacts on nutrient sensing pathways (Marasco et al. 2018; Longo et al. 2021).

Although the effects of adult dietary restriction on ageing are now well recognised, our understanding of how early life nutrition influences longevity is much more limited. Arthropods have been widely used model systems for ageing research, but the relationship between developmental diet and lifespan appears

complex, with inconsistent results reported across studies. Studies investigating how dietary restriction during development influences adult lifespan indeed found both positive (e.g., Joy et al. 2010; May et al. 2015; Hooper et al. 2017; Stefana et al. 2017; Krittika et al. 2019) and negative (e.g., Boggs and Freeman 2005; Runagall-McNaull et al. 2015) effects, as well as no effect (e.g., Tu and Tatar 2003; Zajitschek et al. 2009; Davies et al. 2018) or sex-specific effects (e.g., Hunt et al. 2004; Adler et al. 2013; Kelly et al. 2014; Houslay et al. 2015; Duxbury and Chapman 2020). These inconsistent results may in part be due to the use of different type of nutritional manipulations (e.g., calories restriction or change in macronutrient balance, such as change in the protein to carbohydrate ratio) across studies. For instance, restriction of both yeast and sugar at the larval stage increases adult lifespan in *D. melanogaster* (May et al. 2015), whereas restriction of yeast only has no effect on adult longevity in the same species (Tu and Tatar 2003). The ratio of protein to carbohydrate (i.e., yeast to sugar), not calories *per se*, in the adult diet is particularly important in determining adult longevity in *Drosophila* (Lee et al. 2008). It is thus likely also to influence the effects of developmental diet on longevity. For that matter, there is now growing recognition that increased longevity resulting from dietary restriction is more likely driven by variation in macronutrient content rather than calories in insects and other taxa (Nakagawa et al. 2012; Moatt et al. 2020).

A meta-analysis of experimental studies manipulating early developmental diet (either prenatally or early during postnatal development) only found weak evidence that early life nutrition affects longevity across taxa (English and Uller 2016), with inconsistent patterns reported across studies depending on taxonomic group and timing of nutritional manipulation. Although the authors did not detect any overall impact, the effects of early diet restriction appear more pronounced in vertebrates than in invertebrates and prenatal dietary restriction usually has an opposite effect to early postnatal manipulation, shortening lifespan (English and Uller 2016).

In mammals, laboratory experiments on model species have shown that protein restriction during gestation, through manipulation of the diet of pregnant mothers, is associated with shortened lifespan (Jennings et al. 1999; Sayer et al. 2001; Ozanne and Hales 2004; Langley-Evans and Sculley 2006), while the opposite is observed when restriction happens shortly after birth, during lactation (Jennings et al. 1999; Ozanne and Hales 2004). For example, in both laboratory rats and mice, exposure to a maternal low-protein diet *in utero,* but to a control diet during suckling induces rapid postnatal growth and reduced longevity in male offspring. Conversely, males that are only protein-restricted during the lactation period exhibit slowed neonatal growth and increased lifespan (Jennings et al. 1999; Ozanne and Hales 2004). Interestingly, these males not only live longer than controls and prenatal-restricted males, but are also protected from the life-shortening effects of a fattening diet after weaning (Ozanne and Hales 2004). Further investigations suggest that the mechanisms that could underlie the effects of protein restriction during development on longevity include the alteration of major metabolic pathways such as insulin resistance and antioxidant capacity (Martin-Gronert et al. 2008), changes in the level of oxidative damage, including telomere shortening (Jennings et al. 1999; Tarry-Adkins et al. 2007), and epigenetic modifications (Chen et al. 2010). Overall, rodent

models have highlighted that nutritional restriction might have quite divergent effects depending on when malnutrition is experienced. Protein restriction during early postnatal development might act in a similar manner as dietary restriction in adulthood (i.e., hormetic response, Tarry-Adkins et al. 2007), leading to beneficial effects on longevity, while protein restriction during gestation may permanently program the structure and function of the organism, which may have maladaptive consequences leading to increased susceptibility to metabolic disease and decreased longevity (see Sect. 6.4.3).

Unfortunately, given the practical difficulties in measuring long-term fitness effects of developmental conditions in the wild, studies testing for the association between early nutrition and senescence have almost exclusively been conducted under controlled laboratory conditions and in few short-lived animal models. As such, the impact of developmental nutrition on longevity remains virtually unknown in wild vertebrates. Relevant to this, two recent meta-analyses of published studies looking across species challenged the widely accepted causal relationship between dietary restriction and longevity (Nakagawa et al. 2012; English and Uller 2016). Together, these studies suggest that the accepted paradigm of dietary restriction prolonging lifespan may have little ecological relevance when animals are subject to the pressures of finding food, optimising dietary intake and avoiding predators, and consequently may be an artefact of benign laboratory conditions (Nakagawa et al. 2012; English and Uller 2016) (but see Mautz et al. 2019; Moatt et al. 2020). Wild organisms are selected to maximise reproductive success, not longevity, and thus the ultimate impact of early nutrition on longevity is likely due to trade-offs between fertility and mortality.

6.4.2 *Nutrition-Mediated Trade-Offs Between Longevity and Reproduction*

The impact of early life nutrition on long-term fitness appears complex, because it affects the resources available for growth, reproduction and somatic maintenance (Van Noordwijk and de Jong 1986). As such, nutritional restriction during development is expected to influence life-history strategies and long-term fitness owing to trade-offs in resource allocation (Clark et al. 2015). When food resources are abundant, developing individuals are expected to increase investment across several traits and thus afford to allocate resources to both reproduction and somatic maintenance simultaneously. Many empirical studies have reported a positive relationship between condition-dependent investment in sexually selected traits and longevity across taxa (see meta-analysis by Jennions et al. 2001), suggesting that individuals in good condition can maintain high reproductive performances, whilst avoiding accelerated ageing. Although studies investigating how early life nutrition *per se* might influence this relationship are scarce, a study in the fall field cricket (*Gryllus pennsylvanicus*) showed that males reared on a high-quality diet both invest

more in sexual signalling and have a longer lifespan than males reared on a low-quality diet (Judge et al. 2008). However, this pattern is not observed in another closely related species, the black field cricket (*Teleogryllus commodus*) (Hunt et al. 2004). While female black field crickets reared on a high-protein diet also exhibit a longer lifespan than those reared on a low-protein diet, higher dietary protein levels lead to trade-offs between reproduction and survival in males, which exhibit reduced lifespan due to the costly investment they make in sexual display during early adulthood (Hunt et al. 2004). These cricket species show life-history differences that may explain adaptive investment in signalling (Judge et al. 2008). Regardless, the theory under which high-condition individuals are better able to tolerate sexual signalling costs than low-condition individuals (presumption of the handicap-signalling hypothesis; Zahavi 1975) is not always upheld, and trade-offs between reproduction and somatic maintenance may lead to accelerated ageing under high food availability (Hunt et al. 2004). Aside from the effects of early nutrition on sexual signaling, it is possible that early nutrition affects the strength of sexual selection by affecting mate choice, however evidence for direct effects of early life diet on adult mate preferences is limited. Whilst female black field crickets raised on high protein diets are more sexually responsive than those on low protein diets (Hunt et al. 2005), such effects were not mirrored in similar dietary experiments with fall field crickets (Judge et al. 2014). Furthermore, female zebra finches raised under nutritional restriction do not differ in their song preferences from females raised on an ad lib food supply (Woodgate et al. 2011). Therefore, whether early life diet has long term, consistent effects on adult mate choice preferences, remains largely unclear.

Individuals with access to abundant resources during development may indeed adopt a life-history strategy that maximises early life performances at the expense of late life performances ('live fast, die young' strategy) (Metcalfe and Monaghan 2003). By investing heavily in rapid growth and costly reproductive traits, such individuals may achieve higher reproductive performances in early adulthood, but suffer higher rates of somatic damage and reduced longevity. On the other hand, individuals with access to limited resources during development may experience slower growth, delayed reproduction and increased lifespan. For instance, studies using rodent models have shown that protein restriction during early postnatal life (lactation) leads to delayed sexual maturation (Leonhardt et al. 2003; Zambrano et al. 2005; Guzman et al. 2006) and increased longevity (Jennings et al. 1999; Ozanne and Hales 2004). In arthropods, a valuable demonstration of how early life nutrition may shape life-history strategies comes from an experimental study in the neriid fly (*Telostylinus angusticollis*) where males reared on a nutrient-poor larval diet experience slower development, reach their reproductive peak later in life and live longer than males reared on a nutrient-rich larval diet (Hooper et al. 2017). Although these individuals do not achieve an overall higher mating success than males reared on a poor larval diet, accelerated development and earlier reproduction may provide a substantial fitness advantage in natural populations given the high larval and adult extrinsic mortality risk (Hooper et al. 2017). Although these individuals do not achieve an overall higher mating success compared to males reared on a poor larval

diet, accelerated development and earlier reproduction may provide a substantial fitness advantage in natural populations given the high larval and adult extrinsic mortality risk in the wild (Hooper et al. 2017). Interestingly, these effects of developmental nutrition on life-history strategies have also been shown to occur in females, with similar findings reported in female collared flycatchers (*Ficedula albicollis*) in the wild (Spagopoulou et al. 2020). Although the authors did not manipulate early nutrition *per se*, using brood size manipulations they showed that females raised under good natal conditions exhibit increased early life reproduction at the expense of accelerated ageing (Spagopoulou et al. 2020). In support of such trade-offs, there is robust evidence that compensatory growth in early life is associated with reduced long-term fitness (Metcalfe and Monaghan 2001; Hector and Nakagawa 2012).

Individuals that develop in poor nutritional conditions may not be able to bear the costs associated with accelerated growth and developmental rate or reproduction (Metcalfe and Monaghan 2003). In this case, deferring reproduction and allocating available nutrients to somatic maintenance is often considered to reflect an adaptive resource allocation strategy to increase the chance of surviving challenging period of nutritional deficit (where chances of successful reproduction are low) and reproduce when conditions improve (Shanley and Kirkwood 2000; Partridge et al. 2005). However, poor nutrition during development is not always associated with increased lifespan (Boggs and Freeman 2005; Kasumovic et al. 2009; Runagall-McNaull et al. 2015). For instance, this pattern is not observed in semelparous males of the redback spider (*Latrodectus hasselti*), which only have a single opportunity to mate (Kasumovic et al. 2009): although dietary restriction also leads to increased development time, slower growth and reduced body size (Kasumovic and Andrade 2006), it does not result in increased longevity in this species (Kasumovic et al. 2009). Male redbacks do not feed after maturity and thus only depend on resources acquired and stored as juveniles (Kasumovic et al. 2009). Because they only reproduce once before death, investment of the limited developmental resources into reproduction-related traits should be favoured by selection over investment towards an unnecessary organismal maintenance (Kasumovic 2013). This highlights that species-specific life history and reproductive biology are determinants governing early life nutrition-mediated trade-offs between survival and reproduction. Preservation of reproductive potential over somatic maintenance when developmental resources are limited has also been shown in a butterfly species, the mormon fritillary (*Speyeria mormonia*) (Boggs and Freeman 2005), and in a bird species, the zebra finch (Birkhead et al. 1999).

Similarly, the ultimate impact of early life nutrition may depend on several other factors. First, the conditions experienced beyond development, both in terms of nutritional environment and social context, are likely critical in governing the long-term fitness effects of early life nutrition. Although scarce, some studies have addressed this question by manipulating developmental diets as well as adult food resources and/or adult reproductive opportunities or competitive context. For instance, May et al. (2015) showed that poor larval diet is associated with extended longevity in virgin fruit flies, but the lifespan of mated flies, regardless of their

mating frequencies, is not affected by early life diet (May et al. 2015), indicating that adult reproductive opportunities may mediate the effect of developmental diet on lifespan. Developmental diet also affects patterns of reproduction depending on the adult reproductive environment, with females raised on a poor larval diet having higher reproduction than those raised on a rich diet, either early in life when singly mated or during mid-life when continuously mated (May et al. 2015). More recently, Aw et al. (2018) demonstrated that early life diet of *Drosophilia* alters the fitness landscape for different mitochondrial haplotypes, driven by changes in larval development, probably due to changes in microbiome. These fascinating results suggest that the mitochondrial haplotype can be under selection and that early diet plays an important role in mediating this.

6.4.3 *Early Life Nutrition: Adaptive Response or Developmental Constraints?*

Are phenotypic changes induced by early life nutritional conditions adaptive or a consequence of developmental constraints imposed by resource availability? Several hypotheses linking early life environmental conditions and fitness outcomes have been proposed (Monaghan 2008). The first 'adaptive' explanation is that developmental plasticity induced by early life conditions has immediate ('thrifty phenotype hypothesis'; Hales and Barker 1992, 2001) or long-term ('predictive adaptive response (PAR) hypothesis'; (Gluckman et al. 2005) adaptive advantages. The 'thrifty phenotype hypothesis' proposes that restricted nutritional availability during development causes permanent metabolic changes that enhance early survival in poor nutritional environments (Hales and Barker 1992, 2001). This phenotype has low fat stores and thrives on reduced food availability and has an immediate adaptive advantage (maximising chance of survival during early life nutritional deficit), with possible maladaptive consequences for health later in life if nutritional conditions improve. It has later been suggested, with the 'predictive adaptive response hypothesis', that rather than providing a necessarily immediate advantage, phenotypic changes induced by early life nutritional information are thought to confer a long-term fitness advantage in an anticipated adult environment (Bateson et al. 2004; Gluckman et al. 2005). Under these two environmental matching hypotheses (Monaghan 2008), reproductive performance and survival are expected to be maximised when later-life nutritional conditions match those encountered during development.

Not discounting some notable examples (e.g., Haywood and Perrins 1992; Saastamoinen et al. 2010), general support for the idea that early life nutritional environments indeed match those in later life to increase fitness remains limited (Wells 2007; Uller et al. 2013; Hopwood et al. 2014; Pigeon et al. 2017). Indeed, phenotypic changes can often become maladaptive and lead to fitness costs when developmental and later life nutritional environments are mismatched (Hales and Barker 1992; Gluckman et al. 2005). Thus an offspring's phenotypic response to

early life nutrition may often instead represent an adaptive basis to developmental resource allocation (i.e., constraints) more so than any predictive basis for future environmental selection (Uller et al. 2013). Furthermore, it seems intuitive to suggest that in long-lived animals and humans, early life environmental conditions may not reliably predict future environments sufficiently well to justify an adaptive advantage (Wells 2007). However, it is important to acknowledge that broader support for these predictive matching hypotheses remain constrained by a limited number of studies that have directly manipulated developmental and adult diets simultaneously and measured the fitness consequences of dietary matching or mismatching.

An alternative to these environmental matching adaptive explanations is the 'silver spoon effect' hypothesis (Grafen 1988). This theory predicts that good early nutritional conditions confer a lasting fitness advantage over individuals exposed to poor early conditions (a 'silver spoon' effect; Monaghan 2008). Importantly, fitness advantages arising from silver spoon effects are predicted to persist in individuals regardless of subsequent adult nutritional conditions (Monaghan 2008). There is abundant empirical support for silver spoon effects induced by early life nutrition across a broad range of taxa (Madsen and Shine 2000; Van De Pol et al. 2006; Hopwood et al. 2014; Roberts et al. 2014; Cooper and Kruuk 2018; Spagopoulou et al. 2020). For example, in the zebra finch (Briga et al. 2017), humans (Hayward et al. 2013) and ungulates (Pigeon et al. 2017), good early life nutrition benefits later life fitness components, such as longevity or lifetime reproductive success.

There is also evidence that the silver spoon effect may favour different components of adult fitness. For example, in a recent meta-analysis high-quality early life nutrition produced an overall positive effect for reproductive-related fitness, but not for survival across 14 vertebrate species (Cooper and Kruuk 2018). To some extent, general support for the fitness benefits of the silver spoon effect is constrained by an absence of a large number of studies or that many studies only report the consequence of early life nutritional effects on early- or mid-life performance attributes. Furthermore, recent studies also suggest that a central tenet of silver spoon effects in which benefits to adult fitness are invariant to later life environmental variation is possibly an oversimplification (Pigeon et al. 2019). As extreme environmental variation encountered in later life can better influence, or at least attenuate the effects of early life nutrition on, adult fitness (Pigeon et al. 2019).

6.4.4 Transgenerational Impacts of Diet

Throughout this chapter, we have summarised the multi-facetted ways in which early life nutrition impacts development from the perspective of evolutionary ecology, whilst studiously neglecting much of the biomedical literature which has driven much of this research (e.g., Gluckman and Hanson 2006; Dietrich and Horvath 2013). Evidence, from both experimental studies in animal models and epidemiological studies in humans, indicates that nutrition experienced during early

development, and in particular during embryonic life, can have profound and lasting effects on the structures and functions of an organism, thereby 'programming' the adult phenotype and health status (Langley-Evans 2015). In both human populations and animal models, developmental programming effects of parental nutrition have been primarily investigated in relation to metabolic disturbance, showing that poor parental diet leads to obesity and insulin sensitivity both in the offspring and across generations (Li et al. 2011; Lumey et al. 2015; Masuyama et al. 2015; Jimenez-Chillaron et al. 2016; Zambrano et al. 2016). Under nutrition during foetal development has been associated with heightened risk of a range of conditions, including elevated blood glucose levels, blood pressure, visceral fat deposition and cholesterol levels, together referred to as the 'metabolic syndrome' (McMillen and Robinson 2005) (Fig. 6.3). These conditions are associated with increased adult risk of impaired glucose tolerance (Hales et al. 1991), type-2 diabetes (Hales and Barker 1992) and cardiovascular disease (Barker et al. 1993). Indeed, prenatal maternal stress, undernutrition and maternal diets high in fat, all lead to increased risk of offspring obesity in later life (Levin 2006). But aside from within generation effects, over the last 20 years, mounting evidence indicates that parental diet not only influences offspring development and life-long susceptibility to later-life disease, but that these effects can persist across generations in both humans and animal models (Aiken and Ozanne 2014; Vickers 2014).

In humans, evidence for foetal programming and intergenerational effects of diet mostly comes from studies investigating exposure to severe famines (Painter et al. 2008; Schulz 2010; Li et al. 2011). The classic example of the Dutch famine (1944–1945) has demonstrated association of prenatal nutritional restriction with various adult metabolic dysfunction and cognitive disorders, depending on the timing of exposure to undernutrition during gestation (Roseboom et al. 2011). Furthermore, poor health in later life resulting from prenatal exposure to this famine was found to persist in the next generation (Painter et al. 2008), suggesting epigenetic mechanisms may be involved. Compared with their unexposed same sex siblings, individuals exposed prenatally to the Dutch famine conditions showed reduced DNA methylation of the imprinted insulin-like growth factor 2 gene, 60 years later (Heijmans et al. 2008). This effect was only seen around conception and suggests that very early embryonic development is maximally sensitive to programming effects (Heijmans et al. 2008). Similar impacts of foetal exposure to famine on the adult risk of developing characteristics of the metabolic syndrome have been reported in association with foetal exposure to famine in China (Li et al. 2011) and the Ukraine (Lumey et al. 2015), suggesting the diet-mediated compromised prenatal development effects on adult health is a robust phenomenon. However, the adaptive significance and the relevance of timing still remain subjects of intense debate (Boyce et al. 2020).

A limitation of epidemiological studies is that they only indicate correlational inference and are fraught with cultural confounds. Experimental studies addressing the transgenerational effects of early life diet have used animal models (particularly *Drosophila,* nematodes and rodents) to address how and when parental diet might induce developmental programming in their offspring. In *Drosophila*, parental diet

quality affects offspring development rate (Valtonen et al. 2012), whilst parent dietary sugar content affects body sugar content of F2 offspring (Buescher et al. 2013). Nematodes have proven an efficient model system, with their rapid generation times and simple but plastic dietary requirements, cultured in isogenic lines allowing separation of genetic and environmental influences (Serobyan and Sommer 2017). A network of insulin-like genes has been demonstrated to signal maternal diet to *C. elegans* offspring, whilst broad conservation of these genes suggests the same functional network may operate in vertebrates (Hibshman et al. 2016). These proximate mechanisms may underlie the adverse impact on health, fitness and longevity effects seen when developmental and adult environments are mismatched (Bateson et al. 2004). Meanwhile, rodent models have used different types of maternal dietary manipulations to assess transgenerational impacts of diet (Vickers 2014), including low-protein or low-calorie diets (e.g., see Martínez et al. 2014; Radford et al. 2014; Aiken et al. 2015; Zambrano et al. 2005) and high-fat or obesogenic diets (Gniuli et al. 2008; Pentinat et al. 2010). The responses to maternal overnutrition in sheep (Shasa et al. 2015) and maternal dietary restriction in guinea pigs (Bertram et al. 2008) during the prenatal period both demonstrate the potential transgenerational impact of diet on metabolic syndromes, characterised by elevated glucose levels, basal cortisol levels, altered HPA axis function over F1 and F2 generations. F2 (but not F1) guinea pigs also showed reduced hippocampal volume, suggesting the potential for transgenerational impacts on behaviour (Bertram et al. 2008). However, true transgenerational transmission of phenotype involves demonstrating an impact of maternal diet across more than two generations to control for maternal effects, and convincing experimental vertebrate examples are currently rare (Aiken and Ozanne 2014; Vickers 2014).

Suggested mechanisms for the transgenerational effects of diet include structural effects on tissues and organs, epigenetic programming of gene expression, which mediate neuroendocrine effects or accelerated cellular ageing (Vickers 2014; Aiken et al. 2015). Certainly, there is ample evidence of the impact of maternal nutrition in mammals on HPA function in their offspring (Meaney et al. 2007). In mammals, neuroendocrine mechanisms serve not only to influence metabolism within a generation (Grove et al. 2005), but also mediate metabolic programming across generations through influencing hypothalamic development (Levin 2006; Meaney et al. 2007), possibly through the action of leptin (Simerly 2008). Interestingly for mice, nutritional cues around birth influence insulin resistance and adult body length independent of fat deposition, suggesting that somatic growth is determined by heritable epigenetic factors, rather than absolute resource levels (Dunn and Bale 2009). Finally, maternal choline deficiency has been associated with changes to offspring DNA methylation and is suggested as a dietary micronutrient which may mediate epigenetic effects, although the biological relevance of such effects is unclear (Anderson et al. 2012).

6.5 Conclusions

Throughout this chapter, we have highlighted the multitude of ways in which early life diet can impact on development, with consequences for adult phenotype and ultimately fitness. However, the devil is in the detail, because the effects of any dietary change on development depend on the timing, severity, duration, predictability, caloric and nutrient content, as well as the taxon-specific capacity to compensate. Carefully designed experimental studies of model organisms using controlled dietary manipulations have allowed for teasing apart the physiological pathways underlying the effects of diet on development. We now know a vast amount about how diet impacts development in a few study organisms. However, such inferences rarely allow for interpretation of the adaptive significance of such effects in mediating developmental trade-offs or the impacts on fitness in wild animals (Simpson et al. 2015). Amid such complexity, conceptual frameworks such as nutritional geometry provide a basis for examining the commonalities. Identifying critical or sensitive windows of developmental susceptibility to dietary change seem likely to rely on a sound understanding of the ontogeny of the mechanisms controlling food intake, metabolism and the responses to non-optimal nutritional supplies (Frankenhuis and Walasek 2020). Whilst general patterns of development are understood, for non-model organisms, there are important gaps in our understanding. Mechanistically, the growth in 'omics' approaches for identifying common gene pathways may form the basis for understanding commonalities in physiological drivers or constraints. Integrating transcriptomics with metabolomic approaches may provide important insights into the relevant metabolic pathways. Most promisingly, on-going advances in these areas are likely to be key in helping ameliorate the ultimate consequences of nutritional impacts on animal fitness that can translate into immense and costly public human health (Tilman and Clark 2014) or cohort related impacts in animal populations. For example, therapeutic, lifestyle or animal management related actions that seek to optimise the early life nutritional environment have great potential for increasing human population health or attenuating the actions of global change that compromise domestic or wild animal populations (Monaghan 2008; Tilman and Clark 2014).

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Part III
Anthropocene Opens New Horizons to Reveal the Adaptive Meaning of Developmental Plasticity

Chapter 7
Adaptive and Maladaptive Consequences of Larval Stressors for Metamorphic and Postmetamorphic Traits and Fitness

Robby Stoks, Lizanne Janssens, Vienna Delnat, Janne Swaegers, Nedim Tüzün, and Julie Verheyen

Abstract We synthesized how stressors encountered in the larval stage affect larval growth and development rates, metamorphic traits and eventually carry over across metamorphosis and shape the adult fitness. We mostly refer to case studies on semi-aquatic insects and amphibians, two groups of animals that abruptly switch from an aquatic to a terrestrial habitat during metamorphosis. We focus on two global change-related stressors, warming and pesticide exposure, that are especially relevant in the aquatic habitats occupied by the larvae of semi-aquatic insects and amphibians. Results from our literature review support the traditional view that metamorphosis is not a new beginning and that larval exposure to stressors affects larval growth and development rates and thereby the key metamorphic traits age and size at metamorphosis, eventually affecting adult fitness. While these responses were mostly maladaptive, also cases of likely adaptive responses were identified. We discussed several 'alternative' mechanisms, not mediated through age and size at metamorphosis, that may link larval stressors to adult performance and fitness, including changes in (post-)metamorphic morphology, physiology, gene expression and the gut microbiome. These alternative coupling mechanisms are still understudied and some still need proof of evidence. We summarized the evidence that the implications of carry-over effects across metamorphosis go further than direct fitness consequences of a given larval stressor as these may also change tolerance to stressors encountered in the adult stage. We end by illustrating that the largely unexplored effects of larval stressors on the (post-)metamorphic body composition may have the potential to scale up and change biotic interactions and nutrient fluxes across ecosystems.

R. Stoks (✉) · L. Janssens · V. Delnat · J. Swaegers · N. Tüzün · J. Verheyen
Evolutionary Stress Ecology and Ecotoxicology, University of Leuven, Leuven, Belgium
e-mail: robby.stoks@kuleuven.be

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7.1 Introduction

Many species show a complex life cycle, which can be broadly defined as a cycle where an individual encounters an abrupt ontogenetic transformation of its phenotype (morphology, physiology and behaviour), usually associated with a switch in habitat (Wilbur 1980). Metamorphosis has been considered as a solution to allow life stages to optimally realize their different key functions and to adapt to the intrinsic selective factors of their habitat (Werner 1988; Moran 1994; Rolff et al. 2019). Metamorphosis has fascinated researchers for long time, particularly, whether it can be seen as a new beginning or instead that environmental factors experienced in the larval stage carry over to shape adult fitness (Pechenik 2006). The emerging pattern is that both decoupling and carry-over effects among life stages are present (Rolff et al. 2019).

Arguably, the most studied metamorphic traits are age and size or mass at metamorphosis (hereafter, we will use 'size' to refer to both size and body mass). The age at metamorphosis determines the available time in the adult stage to find a mate and reproduce before the reproductive season ends. An earlier metamorphosis in animals that switch habitats may also imply an escape from larval stressors, such as pond desiccation and larval predators. The size at metamorphosis is another important determinant of adult fitness. For example, in two *Rana* frog species, individuals that metamorphosed at a larger size survived better in the terrestrial stage (Altwegg and Reyer 2003), and *Lestes* damselflies that emerged at a larger mass had a higher lifetime mating success (De Block and Stoks 2005). Given the importance of these metamorphic traits for adult fitness, many studies even used these as fitness proxies to assess the impact of larval stressors on adult fitness. These traits are being driven by two independent biological rates in the larval stage: development rates and growth rates. Development rate refers to the differentiation of the soma and the rate at which organisms go through developmental stages, which is primarily driven by DNA replication. Instead, growth rate is the rate of increase in mass over time and is primarily driven by protein synthesis (van der Have and de Jong 1996). Both rates can be fully decoupled. For example, under time stress larvae of the damselfly *Lestes viridis* increased development rate but not growth rate (Janssens and Stoks 2018).

We here broadly review how environmental factors encountered in the larval stage affect larval growth and development rates, to what extent this has adaptive or maladaptive consequences for the metamorphic traits, and eventually across metamorphosis shape the adult fitness. In addition, we pay attention to alternative mechanisms, not mediated through age and size at metamorphosis, linking larval stressors to fitness across metamorphosis. We broaden the topic of effects of stressors encountered during the larval stage by discussing how such larval stressors may shape the response to adult stressors, thereby creating stressor interaction effects across metamorphosis. Finally, we extend the carry-over effects of larval stressors onto individual fitness toward consequences for biotic interactions and nutrient fluxes across metamorphosis. Throughout this chapter, we mostly refer to case studies on two groups of animals that abruptly switch from an aquatic to a

terrestrial habitat during metamorphosis: semi-aquatic insects (such as midges, mosquitoes, mayflies and odonates) and amphibians. In both groups, the larval stage is entirely dedicated to growth, while the adult stage is also dedicated to reproduction and dispersal (Wilbur 1980). To illustrate the key patterns and mechanisms, we mainly focus on two global change-related stressors, warming and pesticide exposure, that are especially relevant in the aquatic habitats occupied by the larvae of semi-aquatic insects and amphibians (Woodward et al. 2010; Schulz et al. 2021).

7.2 Larval and (Post)Metamorphic Responses to Larval Exposure to Pesticides and Warming

We searched the literature for empirical studies testing for effects of pesticide exposure and warming on metamorphic traits (age and size at metamorphosis) in semi-aquatic insects and amphibians. Within this set of studies, we also extracted, when available, effects on larval growth rates, other larval traits, and post-metamorphic traits. All this information is compiled in Table 7.1.

For the effects of pesticide exposure on metamorphic traits in semi-aquatic insects and amphibians, the following search terms were used in Web of Science: "pesticide and metamorphosis/emergence". This resulted in 472 empirical studies, of which 64 included data on age and size or mass at metamorphosis (see Table 7.1). Among those studies looking at larval growth, more than half (59%) found a negative effect on growth rate, while only one study reported an increase in growth rate when exposed to a pesticide (Wood and Welch 2015) (Fig. 7.1a). Decreases in growth rates can be explained as an energetic cost of being exposed to the pesticide. Pesticide exposure may both reduce energy uptake through reduced foraging (e.g., Teplitsky et al. 2005; Brunelli et al. 2009; Wood and Welch 2015) and increase energy expenditure because of increased investment in detoxification and repair processes (e.g., Monteiro et al. 2019).

For age at metamorphosis, both an earlier and a delayed metamorphosis have been reported after larval pesticide exposure, but the studies reporting a delayed metamorphosis are more than two times as frequent (Fig. 7.1a). Shortening the aquatic larval stage and metamorphosing earlier into the terrestrial stage could be an adaptive strategy to reduce the time spent in the unfavourable, polluted habitat. Instead, delayed metamorphosis could be a direct energetic cost of being exposed to the pesticide, or an adaptive strategy to prolong the larval feeding period, thereby trying to offset the reduced energy budgets to avoid metamorphosis at a smaller size and the associated adult fitness costs. In line with the latter idea, three studies on *Chironomus* midges (Rodrigues et al. 2015a, b; Monteiro et al. 2019) observed a slower larval growth and a delayed metamorphosis in response to pesticide exposure, while there was no difference in mass at metamorphosis. Moreover, the single study on chironomids reporting no pesticide effect on age at metamorphosis

Table 7.1 Empirical studies testing for effects of pollutants and warming on metamorphic traits (age and size at metamorphosis) in semi-aquatic insects and amphibians. Within this set of studies, we also extracted, when available, effects on larval growth rates, other larval traits, and post-metamorphic traits. Green—positive effect, Red—negative effect, Blue—no effect

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Acris blanchardi*	carbaryl		=		higher		=				Boone 2018
Anura	*Acris blanchardi*	glyphosate		higher		higher		=				Boone 2018
Anura	*Acris blanchardi*	imidacloprid		=		higher		=				Boone 2018
Anura	*Acris blanchardi*	malathion		=		=		lower				Hoskins and Boone 2017
Anura	*Anaxyrus terrestris*	atrazine	higher	=		=		=	no effect on activity or swimming speed			Wood and Welch 2015
Anura	*Anaxyrus terrestris*	carbaryl	lower	higher		=		lower	lower activity and swimming speed			Wood and Welch 2015
Anura	*Anaxyrus terrestris*	glyphosate	=	=		=		=	no effect on activity or swimming speed			Wood and Welch 2015
Anura	*Bufo americanus*	atrazine		=		lower		=				Boone and James 2003

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Bufo americanus*	carbaryl		higher		lower in constant hydrope-riods		lower				Boone and James 2003
Anura	*Bufo americanus*	carbaryl		higher		higher in drying hydrope-riods		lower				Boone and James 2003
Anura	*Bufo americanus*	carbaryl		higher		higher		=				Boone 2008
Anura	*Bufo americanus*	carbaryl		higher		lower		=				Boone et al. 2007
Anura	*Bufo americanus*	carbaryl		higher		=		lower		no effect on overwinter survival	no effect on terrestrial growth and mass at spring emergence	Distel and Boone 2009
Anura	*Bufo americanus*	carbaryl		higher at high density		=		=		no effect on overwinter survival	no effect on terrestrial growth and mass at spring emergence	Distel and Boone 2010
Anura	*Bufo americanus*	carbaryl		=		higher	lower	lower				Distel and Boone 2011
Anura	*Bufo americanus*	glyphosate		higher		=		=				Williams et al. 2010

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Bufo americanus*	malathion		higher		higher		=				Boone 2008
Anura	*Bufo americanus*	malathion		higher	lower	lower		=				Smith et al. 2011
Anura	*Bufo bufo*	carbamaze-pine	=	=		higher		=	lower feeding activity		histological effects related to digestion and brains	Bokony et al. 2020
Anura	*Bufo bufo*	endosulfan	lower	higher		lower		lower	respiratory distress, malforma-tions and disturbed swimming			Brunelli et al. 2009
Anura	*Bufo bufo*	glyphosate		higher		lower		lower				Miko et al. 2017
Anura	*Bufo bufo*	glyphosate		higher		lower		lower				Miko et al. 2017
Anura	*Bufo bufo*	terbuthyla-zine	=	=		higher		=	lower feeding activity		histological effects related to digestion and brains	Bokony et al. 2020
Anura	*Bufo cognatus*	propicona-zole/ azoxy-strobin		=	=	=		=				Hartman et al. 2014

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Bufo cognatus*	propicona-zole/ trifloxy-strobin		=	=	=		lower				Hartman et al. 2014
Anura	*Bufo cognatus*	pyraclo-strobin		lower	=	=		=				Hartman et al. 2014
Anura	*Dryophytes versicolor*	malathion		lower		=		lower				Stoler et al. 2017
Anura	*Hoplobatrachus rugulosus*	methomyl	lower	lower	lower			lower			higher MDA, lower glycogen, lower nitric oxide, histological damage to liver, kidneys and gonads	Trachantong et al. 2017
Anura	*Hyla chrysoscelis*	carbaryl		higher		=		=				Boone 2018
Anura	*Hyla chrysoscelis*	carbaryl		lower		=		=	no effect on larval activity			Gaieto et al. 2014
Anura	*Hyla chrysoscelis*	copper sulfate		lower		=		=	no effect on larval activity			Gaieto et al. 2014

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Hyla chrysoscelis*	glyphosate		=		=		=				Boone 2018
Anura	*Hyla chrysoscelis*	imidacloprid		=		higher		=				Boone 2018
Anura	*Hyla chrysoscelis*	malathion		lower		higher		higher	higher activity			Mackey and Boone 2009
Anura	*Hyla chrysoscelis*	malathion		=		lower		=			lower terrestrial growth	Rumschlag and Boone 2015
Anura	*Hyla intermedia*	pyrimethanil	=	higher	=	higher	lower	lower	malformations		malformations	Bernabo et al. 2016
Anura	*Hyla intermedia*	tebuconazole	=	higher	=	higher	lower	lower	malformations		malformations	Bernabo et al. 2016
Anura	*Hyla versicolor*	atrazin		=	higher			=				Relyea 2009
Anura	*Hyla versicolor*	atrazine		=	=	=		lower when combined with predation risk			disturbance of gonadal development	Lafiandra et al. 2008
Anura	*Hyla versicolor*	glyphosate		=		=		=				Williams et al. 2010

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Lithobates clamitans*	carbaryl	=	=		=		=			changes in gene expression	Boone et al. 2013
Anura	*Lithobates clamitans*	malathion		=		lower		=				Stoler et al. 2017
Anura	*Lithobates pipiens*	chlorpyrifos	lower	=	=	=		lower	no effect on activit or brain size, change in brain morphology		no impact on brain size and brain morphology	Woodley et al. 2015
Anura	*Lithobates pipiens*	clothianidin		=	=	=	=	=				Robinson et al. 2019
Anura	*Lithobates pipiens*	thiamethoxam		=	=	=	=	=				Robinson et al. 2019
Anura	*Lithobates sphenocephalus*	atrazine	lower	lower	=	higher	lower	lower	lower surface area			Adelizzi et al. 2019
Anura	*Lithobates sylvaticus*	clothianidin		=	=	=	=	=				Robinson et al. 2019
Anura	*Lithobates sylvaticus*	glyphosate		higher	=	higher				no effect on adult mortality		Gahl et al. 2011
Anura	*Lithobates sylvaticus*	imidacloprid		higher	=	=		lower				Robinson et al. 2017

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Lithobates sylvaticus*	thiamethoxam		=	=	=		=				Robinson et al. 2017
Anura	*Lithobates sylvaticus*	thiamethoxam		=	=	=	=	=				Robinson et al. 2019
Anura	*Litoria raniformes*	atrazine		=	=	=	=	=				Choung et al. 2011
Anura	*Litoria raniformes*	terbufos sulfone		higher	=	=	=	=				Choung et al. 2011
Anura	*Pseudacris triseriata*	glyphosate		higher		=		lower				Williams et al. 2010
Anura	*Rana alvaris*	cypermethrin	=	lower	lower			lower	lower larval hatching succes, abnormal morphology, behavioral abnormalities			Greulich and Pflugmacher 2003
Anura	*Rana dalmatina*	carbama-zepine	=	=		=		=	lower swimming speed		histological effects related to digestion and brains	Bokony et al. 2020
Anura	*Rana dalmatina*	chlorpyrifos		=	=	=		=	malformations	no effect on adult mortality		Bernabo et al. 2011
Anura	*Rana dalmatina*	endosulfan	lower	lower	=	=	lower	lower	malformations			Lavorato et al. 2013

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Rana dalmatina*	terbuthylazine	=	=		=		=	lower swimming speed		histological effects related to digestion and brains	Bokony et al. 2020
Anura	*Rana pipiens*	alachlor		=	=	=		=			no effect on thymus	Hayes et al. 2006
Anura	*Rana pipiens*	atrazine		=	lower	lower		=			thymus damage	Hayes et al. 2006
Anura	*Rana pipiens*	carbaryl		lower		higher		=		no effect on overwinter survival	no effect on terrestrial growth and mass at spring emergence	Distel and Boone 2010
Anura	*Rana pipiens*	carbaryl		lower		higher	=	=				Distel and Boone 2011
Anura	*Rana pipiens*	cyfluthrin		=	lower	=		=			no effect on thymus	Hayes et al. 2006
Anura	*Rana pipiens*	cyhalothrin		=	=	=		=			no effect on thymus	Hayes et al. 2006
Anura	*Rana pipiens*	diazinon		higher	lower			=				Relyea 2009
Anura	*Rana pipiens*	endosulfan		=	higher			lower				Relyea 2009

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Rana pipiens*	glyphosate		higher	lower			lower	malformations at high and medium concentration		disturbance of gonadal development, change in gene expression	Howe et al. 2004
Anura	*Rana pipiens*	malathion		higher at high density		lower		=				Relyea and Diecks 2008
Anura	*Rana pipiens*	metalaxyl		=	=	=		lower			no effect on thymus	Hayes et al. 2006
Anura	*Rana pipiens*	metolachlor		=	=	=		=			thymus damage	Hayes et al. 2006
Anura	*Rana pipiens*	nicosulfuron		=	=	=		=			no effect on thymus	Hayes et al. 2006
Anura	*Rana pipiens*	propiconizole		higher	=	=		=			no effect on thymus	Hayes et al. 2006
Anura	*Rana pipiens*	tebupirimphos		=	lower	lower		=			no effect on thymus	Hayes et al. 2006
Anura	*Rana sphenocephala*	carbaryl		higher		=		higher				Boone et al. 2007
Anura	*Rana sphenocephala*	carbaryl		higher		higher	=	lower			malformations	Bridges 2000
Anura	*Rana sylvatica*	malathion		=		=		=				Relyea and Diecks 2008

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Rana sylvatica*	malathion		higher	higher	higher		=				Smith et al. 2011
Anura	*Rana temporaria*	fenpropimorph	lower	higher when combined with predation risk	lower	lower		lower	lower activity, lower tail length and depth, lower body length			Teplitsky et al. 2005
Anura	*Rana temporaria*	glyphosate		higher	=			lower				Wagner et al. 2017
Anura	*Rhinella arenarum*	atrazine		lower	higher	higher		lower				Brodeur et al. 2013
Anura	*Xenopus tropicalis*	propiconazole	=	lower	=	=	=	=		negative effect on testes in males, no effect on ovaries in females	higher brain aromatase activity, higher LSI in males	Svanholm et al. 2021
Caudata	*Ambystoma macrodactylum*	atrazine		lower	lower	lower		=				Forson and Storfer 2006
Caudata	*Ambystoma maculatum*	carbaryl		higher		lower		lower				Boone et al. 2007

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Caudata	*Ambystoma maculatum*	carbaryl	lower	higher	lower			lower			lower fat content	Metts et al. 2005
Caudata	*Ambystoma opacum*	carbaryl	=	=	lower			lower			no effect on fat content	Metts et al. 2005
Caudata	*Ambystoma texanum*	atrazine		higher in constant hydroperiods		lower in drying hydroperiods		=				Boone and James 2003
Caudata	*Ambystoma texanum*	carbaryl		=		=		lower				Boone and James 2003
Diptera	*Chironomus riparius*	chlorantraniliprole	lower	higher in males		lower in females	lower	lower				Rodrigues et al. 2015a
Diptera	*Chironomus riparius*	chlorpyrifos		=		lower in females			reduction burrowing behaviour		inhibition ChE	Callaghan et al. 2001
Diptera	*Chironomus riparius*	esfenvalerate	lower	higher		=		lower		lower female to male ratio		Rodrigues et al. 2015b
Diptera	*Chironomus riparius*	indoxacarb	lower	higher		=	=	=	increase in GPX,LDH,GST			Monteiro et al. 2019

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Diptera	*Chironomus riparius*	lindane		higher	shorter wing length				reduction burrowing behaviour	reduction in number of eggs laid		Hirthe et al. 2001
Diptera	*Chironomus riparius*	spinosad	lower	higher		=	lower	lower	increase in GPx, LPO, ETS			Monteiro et al. 2019
Diptera	*Culex pipiens*	Bti		higher in males		higher		lower when combined with predation risk		lower r'	no effect on adult fat content or immune response	Op de Beeck et al. 2016
Diptera	*Culex pipiens*	Bti		lower in females		higher		lower when combined with predation risk		lower r'	no effect on adult fat content or immune response	Op de Beeck et al. 2016
Diptera	*Culex pipiens*	chlorpyrifos		lower	=			lower				Tran et al. 2018
Odonata	*Coenagrion puella*	endosulfan	=	higher		=					lower investment in immune function	Campero et al. 2008

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Odonata	*Coenagrion puella*	esfenvalerate	lower	=		lower		lower		no effect on lifespan, reduction in lifetime mating success in females		Tuzun and Stoks 2017
Odonata	*Coenagrion scitulum*	chlorpyrifos	=	=		lower in females	lower	=			wing malformations, decrease in muscle mass, fat content and immune response	Dinh Van et al. 2016a
Odonata	*Coenagrion scitulum*	esfenvalerate	lower	higher		lower		lower			decrease in muscle mass and fat content	Dinh Van et al. 2016b
Odonata	*Enallagma cyathigerum*	chlorpyrifos		lower at 18°C		lower		lower			no effect on cold resistance	Janssens and Stoks 2013
Odonata	*Enallagma cyathigerum*	chlorpyrifos		lower at high food		lower		lower			no effect on cold resistance	Janssens and Stoks 2013

(continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Odonata	*Enallagma cyathigerum*	chlorpyrifos		higher at low food		lower		lower			no effect on cold resistance	Janssens and Stoks 2013
Odonata	*Enallagma cyathigerum*	PFOS		higher		=	lower	lower				Bots et al. 2010
Odonata	*Ischnura elegans*	chlorpyrifos		higher at high latitude at high food		lower		=			lower water content, fat content and immune response, higher Hsp70, no impact on flying ability	Janssens et al. 2014
Odonata	*Ischnura elegans*	chlorpyrifos		lower at high latitude at low food		lower		=			lower water content, fat content and immune response, higher Hsp70, no impact on flying ability	Janssens et al. 2014
Odonata	*Ischnura sp.*	chlorpyrifos	lower	higher		=				no effect on lifespan		Debecker et al. 2016

(continued)

Table 7.1 (continued)

order	species	pollutant	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Odonata	*Lestes sponsa*	esfenvalerate	lower	higher at central latitude		lower	=	=			no effect on adult Ctmax, decrease in fat content and muscle mass	Sniegula et al. 2017
Odonata	*Xanthocnemis zealandica*	carbaryl		=	=		=				no effect on wing size, higher wing asymmetry	Hardersen and Wratten 1998
Odonata	*Xanthocnemis zealandica*	carbaryl		lower	larger wing size		=				higher wing asymmetry	Hardersen 2000
Squamata	*Atheris barbouri*	atrazine		higher		lower		lower				Rohr et al. 2011
Trichoptera	*Brachycentrus americanus*	esfenvalerate		higher	=		lower	lower		lower investment egg mass, lower quality clutches, no effect offsprinfg survival (first two weeks)		Palmquist et al. 2008

(continued)

order	species	warming	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Bufo boreas*	5 °C (27 vs 22 °C)	higher	lower	lower	lower		=				Hayes et al. 1993
Anura	*Discoglossus galganoi*	5 °C (22 vs 17 °C)	higher	lower	lower	lower		=				Alvarez and Nicieza 2002
Anura	*Hoplobatrachus rugulosus*	5 °C (34 °C vs 29 °C)		lower	lower	lower		=				Tang et al. 2020
Anura	*Pelophylax ridibundus*	3 °C (21 °C vs 18 °C)		lower	lower			=				Mosavi et al. 2017
Anura	*Philoria frosti*	5 °C (17 vs 12 °C)	higher (only week2-4)	lower	=	=						Gilbert et al. 2020
Anura	*Pseudacris ornata*	5 °C (20 vs 15 °C) (ambient March 13.7, April 17.0)	higher	lower		lower		higher		Higher adult survival	Lower number of deformities	Harkey and Semlitsch 1988
Anura	*Pseudacris ornata*	5 °C (25 vs 20 °C) (ambient May = 21.6 °C)	=	lower		lower		lower		No effect adult survival	Equal number of deformities	Harkey and Semlitsch 1988
Anura	*Pseudacris ornata*	5 °C (30 vs 25 °C) (ambient June = 24.8 °C)	lower *	=		higher		lower		Lower adult survival	Higher number of deformities	Harkey and Semlitsch 1988

(continued)

Table 7.1 (continued)

order	species	warming	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Anura	*Pseudacris regilla*	3 °C (ambient + 3 °C)	higher	lower	=	=		higher				Regan et al. 2014
Anura	*Rana aurora*	3 °C (ambient + 3 °C)	higher	lower	=	=		=				Regan et al. 2014
Anura	*Rana kukunoris*	3.8 °C (20.3 °C vs 16.5 °C)		lower		lower			Lower feeding and resting frequency, but higher swimming frequency			Zhao et al. 2014
Anura	*Rana lessonae*	5 °C (25 vs 20 °C)	=	lower	lower	lower		higher				Orizaola and Laurila 2008
Anura	*Spea intermon-tana*	3 °C (ambient + 3 °C)	higher	lower	lower	lower		higher				Regan et al. 2014
Anura	*Bufo terrestris*	5 °C (30 vs 25 °C)		lower		lower		=			No effect on sprint speed and endurance; lower metabolic rate only at high food condition	Beck and Congdon 2000

(continued)

order	species	warming	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Caudata	*Desmognathus ochrophaeus*	4 °C (15 vs 11 °C spring/summer ; 11 vs 7 °C fall/winter)	higher (early larval period)	lower		lower		=				Beachy 1995
Caudata	*Eurycea wilderae*	4 °C (16 vs 12 °C spring/summer ; 11 vs 7 °C fall/winter)	=	lower	lower							Beachy 2018
Diptera	*Aedes aegypti*	3 °C (30 vs 27 °C) (lab strains)		=		higher		lower				Rueda et al. 1990
Diptera	*Aedes aegypti*	5 °C (30 vs 25 °C)		lower		higher		=				Rueda et al. 1990
Diptera	*Aedes albopictus*	5 °C (30 vs 25 °C)		lower		lower		=		No effect on longevity		Muturi et al. 2011
Diptera	*Chironomus circumdatus*	5 °C (37 vs 32 °C)	higher	lower		higher		higher				Sankarperuma l and Pandian 1991
Diptera	*Culex pipiens*	4 °C (20 °C vs 24 °C)		lower	lower			lower				Tran et al. 2018
Diptera	*Culex quinquefasciatus*	3 °C (30 vs 27 °C) (lab strains)		=		=		=				Rueda et al. 1990

(continued)

Table 7.1 (continued)

order	species	warming	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Diptera	*Culex quinquefasciatus*	5 °C (30 vs 25 °C)		lower		(M lower; F =) both =		=				Rueda et al. 1990
Diptera	*Culex restuans*	5 °C (30 vs 25 °C)		=		=		=		Longevity 30 < 25 °C		Muturi et al. 2011
Diptera	*Culex tarsalis*	5 °C (35 vs 30 °C)		lower	lower			lower		Longevity 35 < 30 °C		Reisen et al. 1995
Diptera	*Culex pipiens*	5 °C (30 vs 25 °C)		lower	lower			lower				Loetti et al. 2011
Ephemeroptera	*Cloeon dipterum*	3 °C (ambient + 3 °C only during summer)		lower	lower							McKee and Atkinson 2000
Ephemeroptera	*Cloeon dipterum*	3 °C (ambient + 3 °C)		lower	lower							McKee and Atkinson 2000
Ephemeroptera	*Paraleptophlebia bicornuta*	5 °C (Heated Carnes Creek vs Ambient Carnes Creek)		=	=	=		lower				Li et al. 2011

(continued)

order	species	warming	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Odonata	*Ischnura elegans*	4 °C (24 vs 20 °C) *for Swedish	lower	lower		lower	lower	lower		No effect on lifespan		Debecker et al. 2017
Odonata	*Ischnura elegans*	4 °C (ambient + 4 °C)		lower		=	=				Lower flight endurance and mass-corr. flight muscle mass, higher fat content males but not females, no effect flight speed, wing size and shape	Tüzün et al. 2018
Odonata	*Ischnura elegans*	5 °C (25 vs 20 °C)		lower		lower	=				No effect on wing centroid size, area, loading and aspect ratio; total flight duration, max flight height	Arambourou et al. 2017

(continued)

Table 7.1 (continued)

order	species	warming	growth during exposure	age @ meta-mor-phosis	size @ meta-mor-phosis	mass @ meta-mor-phosis	emer-gence succes	larval survival	other phenotypic traits in larva	adult fitness	other phenotypic traits in adult	reference
Odonata	*Pachydiplax longipennis*	2.5 °C (ambient + 2.5 °C)		lower	=			=				McCauley et al. 2015
Odonata	*Pachydiplax longipennis*	5 °C (ambient + 5 °C)		lower	=			lower				McCauley et al. 2015
Trichoptera	*Psychoglypha bella*	5 °C (Heated Carnes Creek vs Ambient Carnes Creek)		lower	=	=		lower				Li et al. 2011

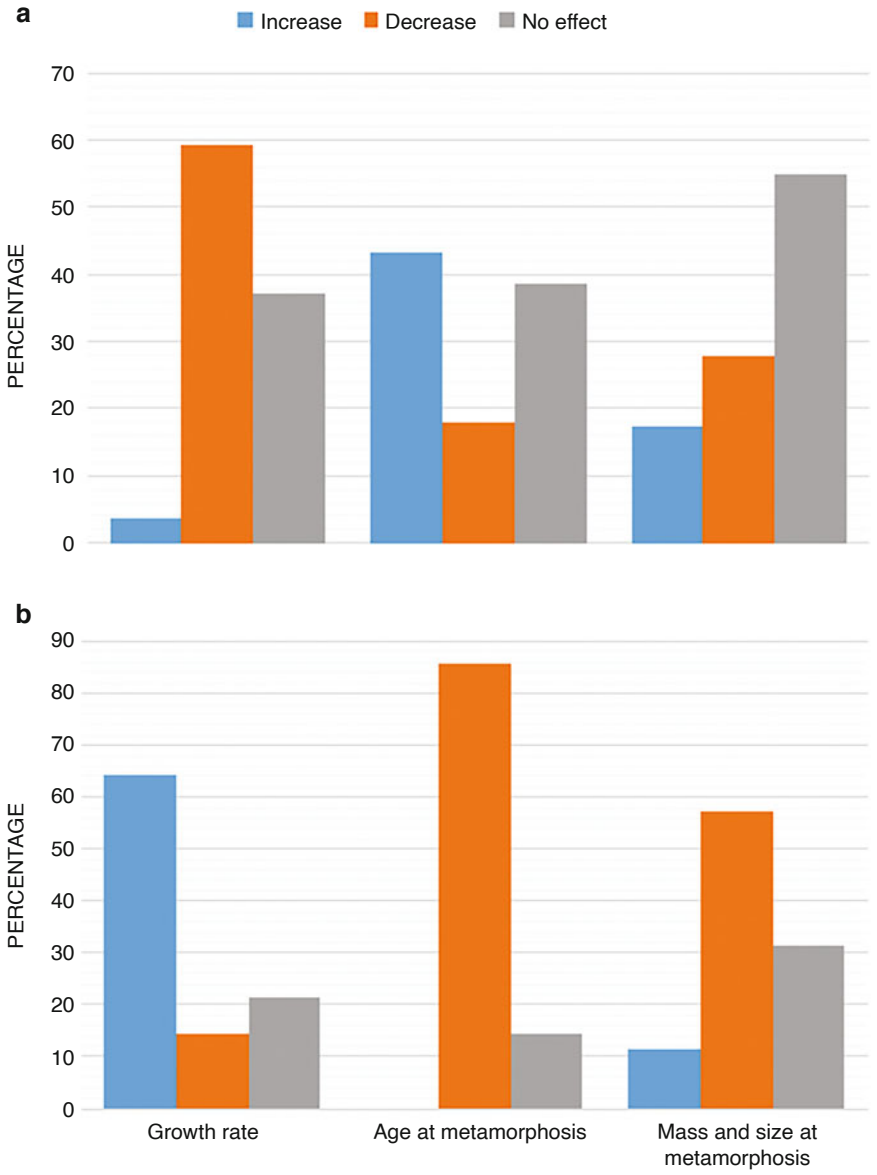

Fig. 7.1 Summary overview of response patterns in semi-aquatic insects and amphibians to larval exposure to (**a**) pesticides and (**b**) warming for a set of life-history traits: larval growth rate, and the two key metamorphic traits (age and size at metamorphosis). The percentages are based on the studies listed in Table 7.1

(Callaghan et al. 2001) showed a decrease in female body mass. A similar pattern of a prolongation of the larval stage that was associated with no reduction of mass at metamorphosis has been observed in damselflies (Campero et al. 2008a; Bots et al. 2010; Debecker et al. 2016) and in frogs (Williams and Semlitsch 2010; Gahl et al. 2011).

In almost half of the studies that quantified size at metamorphosis, this trait was affected by the pesticide treatment in the larval stage (Fig. 7.1a). Both decreases and increases in size at metamorphosis were reported, although decreases were much more frequent. This indicates that compensatory mechanisms are most often absent or not strong enough. Becoming larger after pesticide exposure might seem counterintuitive, but can be caused by high pesticide concentrations that eliminate part of the experimental populations, leading to a higher food abundance for the survivors, which might explain a positive effect on size (e.g., Relyea 2009; Adelizzi et al. 2019). At lethal concentrations, also survival selection may play a role, whereby the weaker, more sensitive individuals are removed from the experiment, and only the strongest, most tolerant individuals, will remain. Alternatively, low pesticide concentrations can have a stimulating, hormetic effect (Costantini et al. 2010; Chap. 2 of this book) on traits, such as activity and food intake (Janssens and Stoks 2013a) leading to an increased energy uptake, which may cause a larger size. Finally, a higher adult size after larval pesticide exposure can also be due to the prolongation of the larval stage (see above) to maximize food intake and growth, whereby animals overcompensated, eventually resulting in a larger size in comparison with the control animals (e.g., Boone 2008).

For the effects of warming on metamorphic traits in semi-aquatic insects and amphibians, the following (combinations of) search terms were used: "warming/temperature and metamorphosis/emergence/eclosion". We limited our overview to studies that compared a control temperature that was explicitly indicated to be the ambient environmental temperature with a treatment with maximum 5 °C warming, the upper level of predicted warming by 2100 under worst-case scenario RCP 8.5 by IPCC (2013). We identified 24 such studies on the effects of warming on metamorphic traits in amphibians and semi-aquatic insects. While all studies looked for effects of warming on age and size at metamorphosis, only 14 focused on larval growth rate. From these 14 studies, more than half (64%) found a warming-induced increase in larval growth rate, and only two studies reported a warming-induced decrease in growth rate [in Swedish populations of the damselfly *Ischnura elegans* (Debecker et al. 2017); in tadpoles of *Pseudacris ornata* (Harkey and Semlitsch 1988)] (Fig. 7.1b). These findings support the idea that many populations in temperate regions are living at ambient temperatures that are below their thermal optimum, hence that mild warming may increase their performance (Deutsch et al. 2008). Higher growth rates under warming are expected when food intake increases more under warming than metabolism (Lemoine and Burkepile 2012). For age at metamorphosis, most studies (86%) reported a decrease (earlier metamorphosis), while none of them found an increase (Fig. 7.1b). This indicates in general a faster larval development under mild warming, as was also found for growth rate. The increases in development rates were apparently often stronger than the increases in growth rates under warming as more than half of the studies (57%) reported

decreases in size at metamorphosis under warming (Fig. 7.1b). This confirms the temperature-size rule (Atkinson 1994; Sheridan and Bickford 2011). In contrast, four studies (14%) found no warming effects on age at metamorphosis (Fig. 7.1b), which might be linked to a strategy to avoid a shorter larval growth period and possible fitness costs caused by metamorphosis at a smaller size. In line with this, warming did not affect age and size at metamorphosis in three of these four studies (Rueda et al. 1990; Li et al. 2011; Muturi et al. 2012). In the fourth study (Harkey and Semlitsch 1988), *Pseudacris* tadpoles compensated their lower larval growth rate under warming by not shortening the larval period (age at metamorphosis was not affected), even resulting in a higher mass at metamorphosis. However, in this case other costs linked to fitness arose. For example, warming reduced larval survival and adult longevity and increased the number of deformities in the adult stage (Harkey and Semlitsch 1988). Possibly, survival selection in the larval stage also played a role, thereby removing all weaker (hence, those more sensitive to warming) individuals. This might also have been the case in *Aedes* mosquitoes, where warming did not affect age, yet increased mass at metamorphosis (Rueda et al. 1990). Intriguingly, in one study on *Chironomus* midges (Sankarperumal and Pandian 1991) warming did accelerate larval development and larval growth rate and also increased mass at metamorphosis and larval survival until metamorphosis.

In several cases we observed that pesticide exposure and warming affected the metamorphic traits in a context-dependent way, indicating that too broad generalizations may be misleading. In some cases, the pesticide-induced changes in metamorphic traits were, for example, only present when the pesticide exposure was combined with an additional larval stressor, such as predation risk (Teplitsky et al. 2005), competition (Relyea and Diecks 2008; Distel and Boone 2010) or time stress (Boone and James 2003). For food stress this even resulted in opposite responses to the pesticide in age at metamorphosis depending on whether food was ad libitum or not (Janssens and Stoks 2013b; Janssens et al. 2014). Another parameter determining the response is the sex with two studies showing that only the males responded with a delayed metamorphosis to larval pesticide exposure (Rodrigues et al. 2015a; Op de Beeck et al. 2016). This may be linked to sex-specific life history strategies.

7.3 Coupling of Traits Across Metamorphosis

According to the adaptive decoupling hypothesis, metamorphosis allows the independent evolution of larval and adult traits to match their key function and habitat by breaking up genetic correlations among the traits between life stages (Moran 1994). Few studies directly studied genetic correlations across metamorphosis, and these showed mixed results (Collet and Fellous 2019). For example, genetic correlations for size-related traits were as strong within the tadpole and frog stages as between these stages. However, there were no genetic correlations across metamorphosis between locomotory traits in the Pacific tree frog *Hyla regilla* (Watkins 2001). In the wood frog *Lithobates* [*Rana*] *sylvaticus* genetic correlations for size-related traits were stronger within the tadpole and frog stages than across metamorphosis,

suggesting some degree of decoupling during metamorphosis (Goedert and Calsbeek 2019). Also the underlying molecular mechanisms of the (de)coupling across life stages are still poorly studied (Collet and Fellous 2019). From *Drosophila* studies we know that both cold and heat tolerance are polygenic traits in both life stages that can have no genetic correlation across stages, suggesting distinct genes code for cold and for heat tolerance in larvae and in adults (Freda et al. 2017, 2019). Similarly, of two melanin-related genes one affected larval and the other adult melanization in a butterfly (Saenko et al. 2012). In a rare study on immune genes, mixed evidence of decoupling was found for two genes coding for defensive antimicrobial peptides: transcription of Diptericin was controlled by the same genetic factors in larvae and adults, while transcription of Drosomycin had no shared genetic control in larvae and adults (Fellous and Lazzaro 2011). Interestingly, also traits that are unrelated at first sight may be genetically coupled across metamorphosis. For example, allelic variation in the 'for' gene not only codes for different levels of foraging activity in the larval stage but also for different dispersal tendencies in the adult stage (Edelsparre et al. 2014).

In the context of whether larval stressors shape adult traits, basically a case of phenotypic plasticity, phenotypic correlations across metamorphosis are more relevant than genetic correlations. Nevertheless, genetic correlations may also mirror phenotypic correlations. While size-related traits typically show positive phenotypic correlations across metamorphosis, this is less obvious for other traits. The few studies that tested whether performance traits are phenotypically correlated across metamorphosis showed no consistent pattern. For example, Watkins (2001) showed tadpole swimming speed and frog jump distance to be positively correlated in the Pacific tree frog *H. regilla*. Yet, swimming performance in tadpoles was shown to be unrelated to jumping performance in froglets in the common frog *R. temporaria* (Johansson et al. 2010). Notably, while decreasing the water level in the tadpole stage (mimicking the time stress imposed by a drying pond) increased the locomotory performance of tadpoles, it negatively affected the one of the froglets.

Behavioural phenotypic trait correlations across metamorphosis have received increasing attention, especially within the context of consistency of inter-individual differences in behaviour (personality) and in suites of behavioural correlations (behavioural syndromes). A recent review revealed that behavioural correlations across metamorphosis are often reported for hemimetabolous insects that undergo complete metamorphosis, but not for holometabolous insects that undergo partial metamorphosis, suggesting behavioural uncoupling across metamorphosis is linked to drastic internal reorganization (Amat et al. 2018). For example, the field cricket *Gryllus integer* had a consistent rank-order for boldness behaviour across metamorphosis (Niemelä et al. 2012), while neither activity nor social behaviour did correlate across metamorphosis in *Drosophila melanogaster* (Anderson et al. 2016). The limited literature on behavioural coupling across metamorphosis in anurans revealed mixed evidence: activity and exploration behaviours in the lake frog *Rana ridibunda* (Wilson and Krause 2012a) and boldness behaviour in the spotted salamander *Ambystoma maculatum* (Koenig and Ousterhout 2018) were consistent across larval and juvenile stages, while boldness and exploration showed no phenotypic correlation across metamorphosis in *R. temporaria* (Brodin et al. 2013b). Ecological

conditions experienced early in life are assumed to play a role in behavioural coupling across metamorphosis (Wilson and Krause 2012b). In a unique study with wood butterfly *Pararge aegeria* populations originating from rural and urban areas, larval activity and boldness were correlated with adult exploration behaviour only in males originating from the harsher urban environments, suggesting that behavioural trait integration across metamorphosis may depend on ecological conditions, and that such patterns can further be sex-specific (Kaiser et al. 2018). While stressors are known to alter the coupling among behavioural traits within the exposed life stage (e.g., contaminants: Brodin et al. 2013a; time stress: Tüzün et al. 2021), it remains to be tested whether early-life (e.g., larval) stressors affect trait coupling across life stages or within the adult stage. Given that trait integration in general (Laughlin and Messier 2015), and specifically among behavioural traits (Sih et al. 2004), has been hypothesized to be adaptive, such carry-over effect of larval stressors would be a novel mechanism linking larval stressors to adult fitness.

7.4 Carry-Over Effects of Larval Stressors on Adult Fitness

Effects of early-life conditions are well known to cross metamorphosis and to impact adult fitness (Harrison et al. 2011; Moore and Martin 2019). We identified 13 studies that recorded not only effects of the larval stressors pesticide exposure and warming on metamorphic traits but also on adult fitness (Table 7.1). Of these, seven studies reported a negative effect on fitness, and only one study showed a positive effect of warming on adult survival (Harkey and Semlitsch 1988). The diverse nature of larval stressors, together with taxa-specific responses to such stressors, makes it challenging to extract general patterns.

A common consequence of exposure to pollutants in the larval stage is decreased survival during metamorphosis, suggesting metamorphosis to be a survival bottleneck in contaminated environments (Table 7.1). For example, exposure to the metal zinc during the larval stage resulted in increased mortality during and after metamorphosis in the damselfly *I. elegans* (Debecker et al. 2017) and during metamorphosis in the mayfly *Neocloeon triangulifer* (Wesner et al. 2014). Intriguingly, neither study reported an increased mortality in the larval stage. Similarly, work on the American toad *Bufo americanus* revealed increased mortality during metamorphosis due to exposure to mercury during the larval stage (Bergeron et al. 2011). While less studied, carry-over effects of larval exposure to pollutants on adult fitness traits often showed negative consequences long after the exposure ended (Table 7.1). Exposure to pollutants early in life reduced lifespan (Debecker et al. 2017) and lifetime mating success (Tüzün and Stoks 2017) in adult damselflies, whereas exposure to copper during the larval stage lowered fecundity in the mosquito *Aedes aegypti* (Perez and Noriega 2014). Interestingly, larval exposure to a stressor may also have unexpected positive effects on adult fitness components. This was shown by a trend for a higher adult cold resistance in *Enallagma cyathigerum* damselflies that were exposed to a pesticide as larvae, possibly due to a pesticide-induced elevation in heat shock protein levels (Janssens and Stoks 2013b).

Surprisingly, little work has been done on carry-over effects of warming in the larval stage on adult fitness-related traits (Table 7.1). The often-observed smaller size at metamorphosis under warming (reflecting the temperature-size rule, Atkinson 1994; Sheridan and Bickford 2011, Table 7.1) may have negative consequences on adult fitness by reducing adult longevity (Reisen 1995) and fecundity. Yet, warming may also negatively affect other fitness-related traits not directly related to size. For example, males of the dragonfly *Pachydiplax longipennis* produced more wing coloration (an intrasexually selected trait that is more advantageous under cooler conditions) when reared under warmer conditions, suggesting this to be a non-adaptive, potentially even maladaptive, response (Lis et al. 2020). Larval exposure of the damselfly *L. viridis* to a higher mean temperature reduced their mass-corrected cold tolerance as adults (Stoks and De Block 2011). In an outdoor mesocosm experiment, 4 °C warming above the ambient temperature in the larval stage resulted in male *I. elegans* damselflies to have a reduced flight performance (a key trait for obtaining mates, foraging and avoiding predation) due to reduced muscle mass, despite no change in mass at metamorphosis (Tüzün et al. 2018). Similarly, a laboratory experiment with the damselfly *I. elegans* revealed reduced flight performance in adults that were exposed to high temperatures as larvae (Arambourou et al. 2017). The effects of warming in the larval stage on flight performance may, however, be complex. A higher larval temperature positively influenced the ability to take off flight, but negatively influenced the ability to sustain flight in the wood tiger moth *Arctia plantaginis* (Galarza et al. 2019). Importantly, carry-over effects of thermal stress may depend on the life stage in which stress was experienced (Kingsolver and Buckley 2020; Ma et al. 2021). For example, thermal stress imposed in the third, but not in the first, larval instar reduced egg production in the diamondback moth *Plutella xylostella* (Zhang et al. 2015).

Aside from pollution and warming, other larval stressors have been linked to fitness consequences in the adult stage. For example, alterations in larval diet have been shown to shape sexual selection on size (in the leaf-footed cactus bug *Narnia femorata*: Gillespie et al. 2014) and male chemical signalling (in the butterfly *Heliconius melpomene*: Darragh et al. 2019), and to reduce lifetime mating success (in the damselfly *L. viridis*: De Block and Stoks 2005) and early-life fecundity (in the butterfly *Bicyclus anynana*: Saastamoinen et al. 2010). Similarly, accelerated larval development in response to time stress resulted in reduced lifespan and mating success in damselflies (*L. viridis*: De Block and Stoks 2005; Janssens and Stoks 2018; *C. puella*: Tüzün and Stoks 2018). Negative effects of larval food stress, however, may be overcome by adult compensatory feeding. For example, food stress during the final larval instar of the damselfly *I. verticalis* affected development rate and adult size, yet fecundity was only determined by adult food stress (Richardson and Baker 1997).

Importantly, evidence emerged that carry-over effects of larval stressors can alter fitness in a sex-specific manner. Exposure to the pesticide propiconazole during the larval stage negatively affected male (testis size, spermatogenesis) but not female reproductive traits (oocytes) after metamorphosis in the frog *Xenopus tropicalis* (Svanholm et al. 2021). In a study conducted under semi-natural conditions, food stress during the larval stage reduced reproductive performance of both sexes in the

Glanville fritillary butterfly *Melitaea cinxia*, yet for the females this was mediated by a reduced pupal mass, while in males this was thought to be mediated by reduced territorial behaviour (Rosa and Saastamoinen 2017). Finally, in a semi-natural study with the damselfly *C. puella*, larval exposure to the pesticide esfenvalerate reduced female but not male lifetime mating success (Tüzün and Stoks 2017), whereas time stress in the larval stage reduced male but not female lifetime mating success (Tüzün and Stoks 2018).

7.5 Alternative Mechanisms Coupling Larval Stressors to Fitness Across Metamorphosis

While it is traditionally assumed that larval stressors are carried over to adult fitness through their effects on age and size at metamorphosis, there is accumulating evidence this is not always the case. An early demonstration of this phenomenon was a study showing that larval food stress and larval time stress did negatively affect adult fitness in the damselfly *L. viridis* but not entirely through effects on age and mass at metamorphosis (De Block and Stoks 2005). A recent meta-analysis revealed this may be rather common in amphibians: while fitness measures, such as survival, reproduction and the prevalence of abnormalities, were negatively affected by altered environments (agriculture, mining and urbanization), age and mass at metamorphosis were largely unaffected (Sievers et al. 2018; but see Edge et al. 2016). This generated a surge of follow-up studies trying to unravel the nature of these carry-over effects that are not mediated through the traditionally studied metamorphic traits. We here give an overview of several types of mechanisms underlying such carry-over effects, and at the same time discuss potential mechanisms for an uncoupling of larval stressors and adult fitness.

One alternative way how larval stressors may shape adult fitness is through changes in morphology. For example, our overview in Table 7.1 shows that larval exposure to pesticides or warming may cause malformations in the adult stage, increases in wing asymmetry, changes in wing shape and reductions in flight muscle mass. All of these can be expected to reduce mobility in the adult stage, thereby reducing escape, foraging and mating performance. Stressor-induced increases in asymmetry may, however, not always bridge metamorphosis. The combination of larval food stress and pesticide stress caused more leg asymmetry in larvae but no longer in adults of the damselfly *C. puella* and neither was the wing asymmetry affected (Campero et al. 2008b). This was explained by metamorphosis itself being stressful and causing a strong increase in asymmetry. Effects of global change factors in the larval stage may also change morphology in such a way that it increases adult performance. For example, rearing of caterpillars on milkweed under elevated CO_2 levels resulted in adults with more elongated wings that are more suitable for elongated flight, hence migration (Decker et al. 2018). In the same study it was shown that parasite infection in the larval stage, however, resulted in rounder wings that are less suitable for sustained flight. Next to this, exposure to larval stressors

may cause a disturbed development of adult organs, such as gonads, thereby impairing reproduction. For example, chronic exposure to the pesticide roundup in tadpoles of *Rana pipiens* resulted in gonadal abnormalities, including cases of intersex (Howe et al. 2004). The phenomenon whereby larval stressors negatively affect the morphology of adult organs is likely general as the development of many organs begins before metamorphosis (e.g., Švácha 1992).

One other important set of mechanisms that may generate carry-over effects on fitness not captured by age and size at metamorphosis operates through changes in the physiology. Best studied in this context is the negative effect of larval stressors on the adult energy budget, which on its turn may negatively affect adult fitness. For example, several studies that exposed larvae to a pesticide demonstrated a lower fat content in the adult stage (Table 7.1). Furthermore, larval stressors have been shown to reduce the adult investment in immune function. For example, exposure of larvae to time stress and to predation risk caused adults of the damselfly *L. viridis* to emerge with a lower activity of the enzyme phenoloxidase that plays a key role in defence against pathogens (Stoks et al. 2006). Similarly, larval exposure of the damselfly *C. puella* to UV resulted in a reduced encapsulation response, a key component of the invertebrate immune response, in the adult stage (Debecker et al. 2015). One other, largely unexplored, but potentially important physiological/molecular mechanism that may link larval stressors to adult fitness is oxidative damage to biomolecules. Oxidative damage occurs when Reactive Oxygen Species (ROS) are not fully balanced by antioxidant defences and thereby generate damage to biomolecules, such as lipids, proteins and DNA (Costantini 2008). This imbalance can be the result of an increased ROS production and/or a decreased antioxidant defence as has been shown, for example, in response to pollutants and to predation risk (Janssens and Stoks 2017). Similarly, larval life history responses demanding an increase in metabolic rate, such as an increase in growth and development rates under time stress, can lead to increased oxidative damage (Gomez-Mestre et al. 2013; Janssens and Stoks 2018; Tüzün et al. 2020). Notably, in animals with a complex life cycle, stressors experienced in the larval stage can cause oxidative damage after metamorphosis (Janssens and Stoks 2018; Burraco et al. 2020). This eventually has been shown to result in a shorter adult lifespan (Janssens and Stoks 2018). Besides direct effects of increased oxidative damage on adult life-history traits, there may also be indirect costs because of increased investment of energy in antioxidant defence and repair, and changes in nutrient allocation and time budgets (Selman et al. 2012; Costantini 2014). In addition, direct costs of oxidative damage to biomolecules, especially proteins, may result in less performant muscles. For example, a higher level of oxidative damage to proteins has been associated with reduced swimming speed in larvae of the damselfly *C. puella*. (Janssens and Stoks 2014). This may potentially contribute to how larval stressors may reduce adult flight performance as observed in damselflies after larval exposure to warming (Arambourou et al. 2017; Tüzün et al. 2018). Despite some case studies illustrating the role of oxidative damage as mechanism coupling the larval and adult stage, metamorphosis may potentially reset oxidative damage. This has been suggested by the decrease in lipid peroxidation during metamorphosis in frogs (Gaupale et al. 2012). A similar pattern might be expected in insects where during metamorphosis larval tissues are

destructed and remodelled and adult tissues are generated (Consoulas et al. 2000). The underlying mechanisms remain unclear, but it is possible that during metamorphosis cells with a high level of oxidative damage may be eliminated and/or oxidative damage may be reduced through activation of repair mechanisms (Geiger et al. 2012; Selman et al. 2012).

One salient new insight in carry-over effects across metamorphosis is that larval stressors may affect gene expression in the adult stage. Studies on this are, however, still rare. For example, 3-day exposure of tadpoles of the green frog *Lithobates clamitans* to carbaryl caused months later changes in mRNA expression in the adult brain for proteins with functional roles in the control of cell growth and signal transduction, indicating long-lasting effects across metamorphosis on brain development (Boone et al. 2013). In another study it was shown that the food stress imposed on larvae of the ladybeetle *Cryptolaemus montrouzieri* resulted in higher expression levels of genes encoding immune- and antioxidant-related enzymes when exposed to starvation and pesticide conditions in adult life (Xie et al. 2015). When different genes underlie traits in larvae and adults, this may explain why environmental factors shaping a larval trait not necessarily affect the adult trait. This was likely the reason why rearing larvae of the wood tiger moth *Arctia plantaginis* under 9 °C warming resulted in a lower melanization of both the larval and adult bodies, while the wing melanization was not affected (Galarza et al. 2019). Moreover, the uncoupling of larval and wing melanization could be driven by the fact that in insects adult structures, such as wings and legs, derive from separate clumps of cells (imaginal disks) and that differences in timing of induction of different imaginal disks thus may cause independent development of body parts (Whitman and Agrawal 2009). Next to gene expression, larval stressors may also affect pre-mRNA splicing of genes and thereby affect adult performance. The few studies on this topic support this idea. For example, rearing of larvae of the fall armyworm moth *Spodoptera frugiperda* under food stress resulted in alternative splicing of the flight muscle gene troponin-t to form protein isoforms that were associated with reduced muscle performance and energy consumption, independently from the muscle mass (Marden et al. 2008).

One specific way how larval stressors may shape adult gene expression is through epigenetic mechanisms, i.e., through molecules that modify DNA accessibility to enzymes and therefore can up- or downregulate gene expression (McCaw et al. 2020). Epigenetic mechanisms are considered as a mediator of the interaction between the environment, the genome and development (McCaw et al. 2020; Chap. 1 of this book). Indeed, epigenetic mechanisms are environmentally sensitive and have the capacity to be stable, thereby allowing organisms to adapt to environmental changes and mediate environmental memory across life stages (D'Urso and Brickner 2014). For example, in the three-spined stickleback *Gasterosteus aculeatus* the effects of early-life exposure to warming in larvae affected temperature acclimation in adults through DNA methylation (Metzger and Schulte 2018). In this study, it was found that 25% of the differentially methylated regions associated with variation in larval developmental temperature were also differentially methylated in response to temperature acclimation in adults. In rodents and humans, exposure to endocrine disruptors in early-life has been shown to alter, respectively, reproduction

and disease susceptibility in adults through epigenetic modifications (Mirbahai and Chipman 2014). In amphibians, exposure to stress hormones early in development can cause changes in behaviour and physiology of the adult and is likely mediated through epigenetic molecules (Denver 2021).

Another promising candidate mechanism linking larval stressors to adult fitness are changes in the gut microbiome. Evidence is accumulating that the gut microbiome may have a large influence on the phenotype of its host and its tolerance to stressors (Hammer and Moran 2019; Lynch and Hsiao 2019). Both warming (e.g., Bestion et al. 2017) and toxicants (e.g., Fong et al. 2019) can induce changes in the gut microbiome that may harm or benefit the host, also with respect to its tolerance (e.g., Fong et al. 2019). The gut microbiome composition may differ before and after metamorphosis. For example, the relative abundance of gut microbial taxa showed distinctive differences between larvae, metamorphic animals and juveniles in wood frogs (*Lithobates [Rana] sylvaticus*), green frogs (*L. clamitans*) and bullfrogs (*L. catesbeianus*) (Warne et al. 2017). Similarly, larvae, pupae and adults of the mosquito *Anopheles gambiae* showed distinctive gut community structures (Wang et al. 2011). Possible explanations for these shifts in microbiome composition are the obligate fasting that larval amphibians and semi-aquatic insects undergo during metamorphosis (Warne et al. 2017), and ontogenetic shifts in diet (Kohl et al. 2014; Kohl and Carey 2016). The restructuring of the gut microbiota during metamorphosis may be important and has been suggested to determine survival during metamorphosis in the giant spiny frog *Paa spinosa* (Long et al. 2020). Nevertheless, changes in gut microbiomes during early life can shape metabolism and immunity of adult animals (Arrieta et al. 2014; Cox et al. 2014). For example, early-life disruption of the microbiota of tadpoles of the Cuban tree frog *Osteopilus septentrionalis* by using antibiotics resulted in a lower adult resistance to parasites (Knutie et al. 2017). Notably, this carry-over effect occurred despite no changes in the adult gut microbiome, suggesting it was mediated by effects on immune system development caused by dysbiosis of the tadpole gut microbiome. In a companion study on the same frog species, early-life exposure to the herbicide atrazine reduced the tolerance to a chytrid fungus but did not affect the gut microbiome of tadpoles and adults, indicating the effect of atrazine on infection risk was not mediated by host-associated microbiota (Knutie et al. 2018). However, host-associated microbes did seem important in host resistance to the fungus because the early-life microbiota, likely by playing a role during immune system development, predicted adult infection risk.

7.6 Interactions Between Stressors Across Metamorphosis

Larval stressors can also impact the response to adult stressors. Although the research on this topic is rather limited, interactions between responses to stressors across metamorphosis have been shown in several species, including anurans and insects. In Table 7.2, six studies investigating the combined impact of larval and adult stressors on adult life history and physiology are summarized. These studies

Table 7.2 Overview of studies investigating interactions between larval and adult stressors in semi-aquatic insects and amphibians

Order	Larval stressor	Adult stressor	Interaction type	Response variable	References
Anura	Pesticide mixture	Fungal exposure (Bd)	Additive	Survival	Buck et al. (2015)
	Pesticide mixture	Fungal exposure (Bd)	Synergism	Bd load	Buck et al. (2015)
Anura	Fungicide	Fungal exposure (Bd)	Synergism	Survival	Rohr et al. (2017)
	Fungicide	Fungal exposure (Bd)	Synergism	Bd load	Rohr et al. (2017)
Diptera	Temperature	Plasmodium infection	Antagonism at 37 °C and 39 °C; synergism at 40 °C	Percentage oocyst positive	Raghavendra et al. (2010)
	Temperature	Plasmodium infection	Antagonism	Oocyst plasmodium load	Raghavendra et al. (2010)
Diptera	Insecticide	Temperature	Synergism	Survival	Tran et al. (2020)
Lepidoptera	Food stress	Food stress	Synergism at low and medium adult temperature; additive at high adult temperature	Body mass	Karl et al. (2011)
	Food stress	Food stress	Synergism at low adult temperature; additive at medium and high adult temperature	Fat content	Karl et al. (2011)
	Food stress	Food stress	Additive	Haemocytes	Karl et al. (2011)
	Food stress	Food stress	Additive at low and medium adult temperature; antagonism at high adult temperature	PO activity	Karl et al. (2011)
	Food stress	Temperature stress	Additive at low temperature; synergism at high temperature	Body mass	Karl et al. (2011)
	Food stress	Temperature stress	Synergism	Fat content	Karl et al. (2011)
	Food stress	Temperature stress	Antagonism	Haemocytes	Karl et al. (2011)
	Food stress	Temperature stress	Antagonism at low temperature, synergism at high temperature	PO activity	Karl et al. (2011)

(continued)

Table 7.2 (continued)

Order	Larval stressor	Adult stressor	Interaction type	Response variable	References
Odonata	Insecticide	Heat wave	Antagonism	Fat content	Janssens et al. (2014)
	Insecticide	Heat wave	Antagonism	Hsp70	Janssens et al. (2014)
	Insecticide	Heat wave	Synergism	PO activity	Janssens et al. (2014)
	Food stress	Heat wave	Additive	Fat content	Janssens et al. (2014)
	Food stress	Heat wave	Antagonism	Hsp70	Janssens et al. (2014)
	Food stress	Heat wave	Antagonism	PO activity	Janssens et al. (2014)

used as larval stressors pesticide exposure, food stress and temperature, while the adult stressors were pathogen infections, food stress and temperature. In most cases (41%) reported in Table 7.2, the larval and adult stressors magnified each other's negative effects, so-called synergistic interaction effects. Yet, also antagonistic interactions (33%) whereby, for example, the upregulation of a defence mechanism to an adult stressor is lower after exposure to a larval stressor, may negatively impact fitness. We here provide a more detailed description of all studies of Table 7.2, thereby discussing the underlying mechanisms.

When exposed to a pesticide as tadpoles, anurans showed a synergistic increase in fungal load when infected with a chytrid fungus after metamorphosis (Buck et al. 2015; Rohr et al. 2017), which for the Cuban tree frog *O. septentrionalis* even resulted in a synergistic increase in mortality (Rohr et al. 2017). Interestingly, in mosquitoes, the opposite pattern was observed between larval temperature stress and adult plasmodium infection, hereby the plasmodium load was lower in animals exposed to the high temperature as larvae (Raghavendra et al. 2010). The reason for this different stressor interaction type could be that pesticide exposure typically reduces the immune response (Janssens et al. 2014; Brandt et al. 2020) leading to a higher sensitivity to pathogens, while higher temperatures are often linked to higher enzymatic activities including those related to the immune defence (Wojda 2017). In damselflies, larval pesticide exposure followed by adult heat exposure resulted in antagonistic interactions especially in traits linked to defence, whereby the heat-induced increase in Hsp70 levels was smaller in adults previously exposed to the pesticide (Janssens et al. 2014). These antagonistic interactions are most likely the result of energetic constraints, whereby exposure to the larval stressor already asked a profound energy investment in defence, leading little additional energy to be invested in defence against the adult stressor. Similarly, the pesticide-induced reduction in phenoloxidase activity was stronger in heat-exposed adults, which again can be seen as a physiological, energetic cost of the stress exposure (Janssens

et al. 2014). In mosquitoes, the interaction between larval pesticide exposure and a higher adult temperature even resulted in a synergistic increase in mortality (Tran et al. 2020). Besides pesticide stress, also suboptimal larval food conditions are shown to interact with adult stressors. For example, in the butterfly *Bicyclus anynana* a temperature-dependent synergistic interaction between larval and adult food stress was shown on body mass and fat content, whereby the two food stressors enhanced each other especially at low and intermediate temperatures (Karl et al. 2011). In the same study also the interaction between larval food stress and adult temperature was investigated whereby for body mass, fat content and phenoloxidase activity synergistic interactions were found between larval food stress and adult temperature stress.

7.7 Consequences of Carry-Over Effects of Larval Exposure to Stressors for Biotic Interactions and Nutrient Fluxes Across Metamorphosis

Stressors experienced during the larval stage may, by changing the age, body mass and body composition at metamorphosis, not only affect the adult fitness but also biotic interactions and nutrient fluxes across metamorphosis. In case of semi-aquatic insects and amphibians, this may cause carry-over effects of stressors in the aquatic larval environment into the receiving terrestrial environment (e.g., Paetzold et al. 2011; reviewed in Schindler and Smits 2017). Two important aspects of the body composition at metamorphosis that can be important for their nutritional quality as food for terrestrial consumers are the stoichiometric composition (elemental composition, mainly of carbon, nitrogen and phosphorus) and the content of polyunsaturated fatty acids (PUFAs) (Schindler and Smits 2017). Particularly for semi-aquatic insects, but also for amphibians, it is well-known that they transport aquatic-derived materials of high nutritional quality (stoichiometric composition: Schindler and Smits 2017; high PUFA content: Martin-Creuzburg et al. 2017; Twining et al. 2018b; Fritz et al. 2019) to terrestrial ecosystems and are therefore ecologically very important fluxes, called aquatic subsidies (Schindler and Smits 2017). Terrestrial consumers, both vertebrates (e.g., birds and bats) and invertebrates (e.g., spiders) depend on these aquatic subsidies for their high PUFA content that plays an important physiological role going from immune function to neural development (Twining et al. 2016a). This is especially true because terrestrial consumers synthesize long-chain omega-3 PUFAs (LC-PUFAs) at a low efficiency (e.g., in Tree Swallows: Twining et al. 2018a) and have low levels of the needed precursor omega-3 PUFA alpha-linolenic acid (Twining et al. 2016b). PUFA derived from semi-aquatic insects may therefore be important for the fitness of terrestrial consumers. For example, *Tigrosa* wolf spiders living in wetlands where they can consume aquatic subsidies had higher levels of aquatically derived LC-PUFAs and a better immune function than spiders living in uplands (Fritz et al. 2017).

By changing the age at metamorphosis, larval stressors, such as warming and contaminants (Table 7.1), may cause critical changes in the timing of these fluxes. This may result in temporal mismatches with terrestrial consumers relying on these aquatic subsidies (O'Gorman 2016), eventually leading to altered growth and development rates in terrestrial predators (e.g., in spiders: Marczak and Richardson 2008). Larval stressors may also change the quality of these fluxes both by affecting the stoichiometric content and the PUFA content at and after metamorphosis. For example, in a natural study with experimental pond systems, mild 4 °C warming resulted in decreased body phosphorus content in emergent frogs (*Rana temporaria*: Norlin et al. 2016). As a special case of changes in body composition, contaminants to which larvae were exposed may cross metamorphosis and end up in the adult bodies (Al-Jaibachi et al. 2018; Bundschuh et al. 2019; Previšić et al. 2021). In semi-aquatic insects and amphibians, this may cause transfer of contaminants across ecosystem boundaries. For example, the Chinese mantis (*Tenodera aridifolia sinensis*) accumulated arsenic after feeding on mosquito (*Culex tarsalis*) adults that were exposed to arsenic as larvae (Mogren et al. 2013). Similarly, terrestrial spiders have been shown to accumulate persistent bioaccumulative polychlorinated biphenyls (Walters et al. 2008), methyl mercury (Tweedy et al. 2013), mercury (Pennuto and Smith 2015), and metals (Kraus et al. 2014) through feeding on semi-aquatic insects exposed to these contaminants.

In addition, larval stressors may reduce the quantity of aquatic subsidies by negatively impacting larval survival and emergence success, hence by reducing the numbers and biomass of emerging semi-aquatic insects and amphibians. For example, the numbers and biomass of emerging semi-aquatic insects decreased with increasing levels of trace metals (Kraus et al. 2014) and of the pesticide bifenthrin (Rogers et al. 2016). Contaminant-induced reductions in the quantity of aquatic subsidies have been shown to negatively affect terrestrial predators. These negative effects included declines of insectivorous birds (Manning and Sullivan 2021), lowered spider species abundance and richness (Graf et al. 2019), spider population declines (Paetzold et al. 2011) and spider community structure shifts (Paetzold et al. 2011; Graf et al. 2019), even while numbers of available terrestrial prey organisms remained the same (Paetzold et al. 2011). Furthermore, when aquatic subsidies are scarce, this may cause terrestrial predators, such as spiders, to switch to terrestrial prey, such as grasshoppers, thereby impacting herbivory (e.g., Graf et al. 2017).

7.8 Conclusions and Future Directions

Results from our literature review, mainly based on semi-aquatic insects and amphibians, provide ample evidence for the idea that early life stressors are an important source of phenotypic diversity. Moreover, they support the traditional view whereby larval exposure to stressors, i.e., pesticides and warming, affects larval

growth and development rates and thereby the key metamorphic traits age and size at metamorphosis, eventually resulting in effects on adult fitness. While these responses were mostly maladaptive, also cases of likely adaptive responses were identified. As such our overview matches a more general recent meta-analysis concluding that environmental stressors encountered during early life may negatively affect the adult phenotype and performance, but may also be neutral and even positive (Eyck et al. 2019). In their meta-analysis, there was large variation in the responses and little of this variation could be explained (Eyck et al. 2019). In line with this, we documented several cases of context-dependency whereby the (post)-metamorphic response critically depended on factors, such as sex, population of origin and timing of exposure to the larval stressor.

In addition, we also identified several 'alternative' mechanisms that may link larval stressors to adult performance and fitness, including changes in (post-) metamorphic morphology, physiology, gene expression and the gut microbiome. These alternative coupling mechanisms are still understudied and some still need proof of evidence. Most likely, several of the 'traditional' and 'alternative' mechanisms co-occur together, yet we currently do not know their relative importance in shaping adult fitness and to what extent age and size at metamorphosis are good proxies for adult fitness. This asks for studies that in an integrated way assess multiple mechanisms. Such studies would bring crucial insights not only into the coupling but also in the observed cases of uncoupling between larval and adult life stages. One fruitful avenue for further research would be to integrate in such research programs also a modelling component, as illustrated by a dynamic energy budget model that captured the fate of acquired and stored nutrients across metamorphosis (Llandres et al. 2015).

Whatever the coupling mechanism, the emerging view of the here synthesized studies is that metamorphosis is not a new beginning (Pechenik 2006) and that most often larval stressors affect metamorphic traits that have the potential to translate into a changed adult fitness. Moreover, there is, admittedly still limited, evidence that the implications of carry-over effects across metamorphosis go further than direct fitness consequences of that larval stressor and may also imply changed tolerance to stressors encountered in the adult stage. In general, this implies that to fully understand whether and how animals respond to adult stressors we need to know their larval history of exposure to stressors. For the same reason, this also means that a large part of the variation in adult fitness can only be understood when knowing previous exposure to fitness. Moreover, we have documented that the largely unexplored effects of larval stressors on the (post-)metamorphic body composition may go beyond effects for that individual and have the potential to scale up and change biotic interactions and nutrient fluxes across ecosystems.

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Chapter 8
Plastic Aliens: Developmental Plasticity and the Spread of Invasive Species

Giulia Cordeschi, David Costantini, and Daniele Canestrelli

Abstract Biological invasions are one of the worst threats to biodiversity conservation, ecosystem services and functionality, and human health. However, of the high number of organisms that are transported and introduced outside their native range, only a subset of them can survive, establish and spread in the novel area, becoming invasive. What determines the ability of an alien animal species to become invasive? There is an increasing awareness that the answer to this longstanding and crucial question is highly multifactorial, with some factors already well-discerned, and some not yet elucidated. In this book chapter, we focus on developmental plasticity, the permanent change in the developmental trajectory adopted by an organism in response to gene–environment interactions. Developmental plasticity is an important adaptive response to the obvious variability of biotic and abiotic environmental conditions over time. Yet, it can also promote the invasion of novel habitats, by favouring the optimal match between individual phenotypes and the new environment, during the early steps of an invasion. By relying on the available literature and focusing on animal invasions, we analyse the adaptive advantages conferred by developmental plasticity (i) in dealing with the new biotic and abiotic environment during the stage of introduction, (ii) in terms of reproductive rate and population growth, two crucial processes for overcoming the stages of establishment and (iii) in dispersal traits promoting the spread in the new environment. We conclude that, although acknowledged in previous literature, the actual contribution of developmental plasticity to the shaping of the *ideal invader* might have been underrated.

G. Cordeschi · D. Canestrelli (✉)
Department of Ecological and Biological Science, University of Tuscia, Viterbo, Italy
e-mail: canestrelli@unitus.it

D. Costantini
Unité Physiologie moléculaire et adaptation (PhyMA), Muséum National d'Histoire Naturelle, CNRS, CP32, Paris, France

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8.1 Biological Invasion

Biological invasion is a process characterised by the spread of a species outside of its native range (Richardson and Pyšek 2006). It is considered one of the worst threats to biodiversity conservation, ecosystem stability and functions, and a wide range of ecosystem services (Prentis et al. 2008). Following its introduction in a non-native area, an alien species is considered invasive if it spreads in the new environments and has serious negative ecological and economic consequences (Lockwood et al. 2013; see Glossary).

A non-native species must pass through three stages before inflicting ecological and economic damages (Lockwood et al. 2013) and be considered invasive. First, an alien species is a group of individuals transported to a new area during the first stage of the introduction. Then, these individuals must be able to establish a self-sustaining population in the new environment, otherwise they will face extinction. Following a successful establishment, the new non-native population may remain scarcely abundant and limited in distribution over the area (e.g., Andreone et al. 2016), or it may grow, triggering the spread stage. Typically, only when the new population reaches the last stage and becomes widely distributed and abundant it can be defined as invasive (see Glossary). It is at this stage that the alien species can cause environmental and economic damages. However, at each stage of the process, the invasion may fail (Hui and Richardson 2017; Blackburn et al. 2011). The invasion success depends on several biotic and abiotic factors, such as the invasive propagule pressure, the biological and ecological traits of the invader, the degree of matching between pre-existing abiotic conditions of the native habitat and those of the invaded ecosystem, and the interactions between the invading organism and the native species (Richardson and Pyšek 2006). Eventually, only a tiny percentage (ca. 10%) of the population of an introduced species becomes established, and even a smaller proportion of individuals (ca. 10%) becomes invasive (*The tens rule*, Williamson and Fitter 1996).

The outcomes of an invasion can be observed and evaluated at the individual, population, community or ecosystem level. The arrival of an invader may have several individual-level impacts that can alter several phenotypic traits of native species in response to novel predatory or competitive interactions (Parker et al. 1999). One example comes from the interaction between the Fire ant (*Solenopsis invicta*), a widely diffused invasive species, and the native eastern fence lizard (*Sceloporus undulatus*) in the United States of America. The invasive fire ants use to attack lizards, get close to their mound, swarm onto the lizard's body, and stitch the soft skin under the dorsal scales. Lizards can escape or shake off the ants with a body-twitch behaviour. Lizards with a long time of coexistence with the fire ants flee and body-twitch more often when attacked, and have longer hind limbs, making their reactions more efficient (Langkilde 2009). Thus, the invasive fire ant worked as a selective pressure, driving morphological and behavioural modifications of lizards.

Invasive species may cause changes in abundance, distribution, structure, or population growth rate of native species (Parker et al. 1999). They may also trigger

local extinction of one or more native species, as often seen on islands and other isolated biogeographic contexts (Lockwood et al. 2013). One example is the introduction of the Nile perch (*Lates niloticus*) into Lake Victoria in 1950s. Thanks to the peculiar and distinctive characteristics of the Lake Victoria, it has been the evolutionary cradle for the origin of more than 400 species of cichlid fishes (Greenwood 1981; Witte et al. 1992; Seehausen 2000). The introduction of a novel predator, like the Nile perch, led to (i) changes in the community composition, (ii) the complete extinction of half of the native cichlid species (Witte et al. 1992), and (iii) severe damages and losses to the local economy (Baskin 1992).

In fact, invasive alien species can dramatically impact ecosystem processes that are critical to human well-being. Ecosystem changes may cause the loss of agricultural and fishery products and even the disruption of ecosystem services, such as climate stabilisation, availability of drinking water and pollination (Pejchar and Mooney 2009). For example, the zebra mussel (*Dreissena polymorpha*), introduced in various aquatic environments due to its filter-feeding capacities, caused severe ecological and economic damages, such as coating boats and docks and clogging water supply outlets of municipalities and hydroelectric plants (Kovalak et al. 1993).

What makes an introduced alien species a successful invader? Following the seminal book by Charles S. Elton (1958) *The ecology of invasions by animals and plants*, the number of studies on biological invasions has increased exponentially in the last 60 years (Richardson and Pyšek 2008), and many studies have sought to answer the question of why successful invaders are so successful. Baker (1965, 1974) identified several traits describing what he defined as the "ideal weed", arguing that species showing these traits are more likely to be invasive than species that show them to a lesser extent. In Baker's view, traits promoting invasiveness include the ability to reproduce both asexually and sexually, rapid growth from seed to sexual maturity and, in particular, high adaptability to environmental stress along with high tolerance to environmental heterogeneity. Later studies on plants have identified other characteristics associated with reproductive potential, vegetative reproduction, dispersal, life-form and competitiveness as essential features of a successful invader (Forcella et al. 1986; Noble 1989; Roy 1990; Pysek et al. 1995; Rejmanek 1995; Thompson et al. 1995; Crawley et al. 1996; Reichard and Hamilton 1997; Pysek and Richardson 2007).

In this book chapter, we point out that the stages of growth and development are critical windows during which much of the future invasion capabilities are determined. We will focus mainly on two features proposed to describe the ideal invader: developmental plasticity and growth rate. Phenotypic plasticity can be broadly defined as the ability of a genotype to produce different phenotypes in response to environmental changes (West-Eberhard 1989; Agrawal 2001; DeWitt and Scheiner 2004; Pigliucci et al. 2006). Although initially applied only to morphological traits (Schlichting and Pigliucci 1998), it is now increasingly recognised that other traits (e.g., physiology, behaviour, life-history) can also be modified in response to an environmental stimulus (Whitman and Ananthakrishnan 2009). Phenotypic plasticity is closely tied to development conditions, since early life is a temporal window during which the phenotype is very sensitive to environmental stimuli. The term

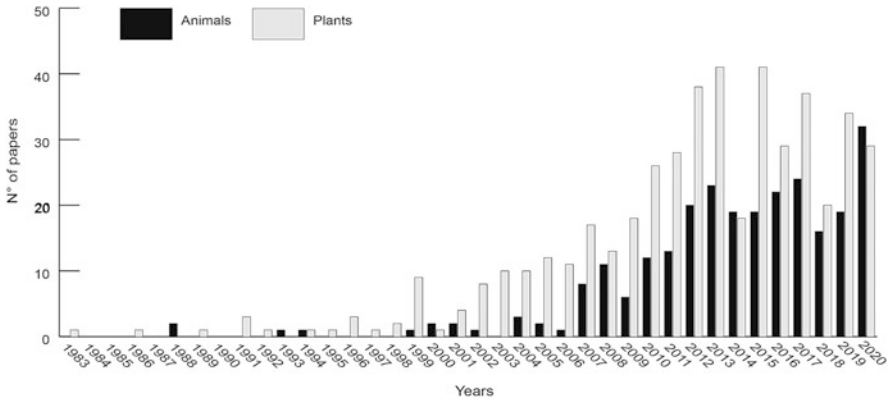

Fig. 8.1 Number of studies on developmental plasticity in the biological invasion process published from 1983 to 2020

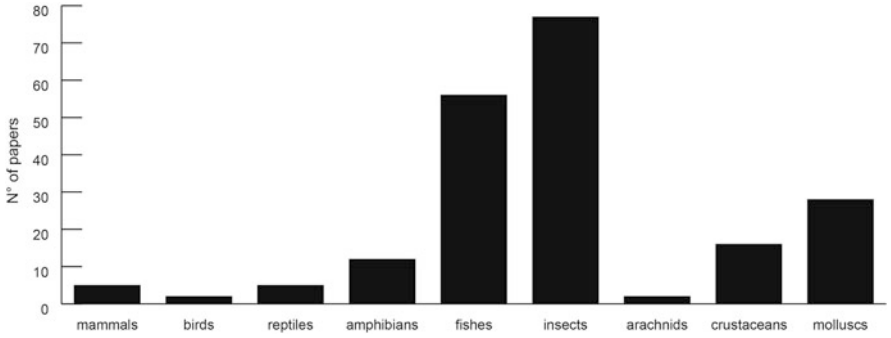

Fig. 8.2 Number of studies on developmental plasticity in invasive animal species

developmental plasticity refers specifically to those phenotypic changes that occur during development to adjust the phenotype to the prevailing environmental conditions (Davis and Wund 2016; West-Eberhard 2005).

The idea that developmental plasticity plays a role in the success of an invasion goes back to Baker's studies (Baker 1965). In the last 30 years, the number of scientific studies on the role of developmental plasticity in biological invasions has dramatically increased (Box 8.1, Fig. 8.1), particularly on invasive plant species (Daehler 2003; Richardson and Pyšek 2006; Funk 2008; Hulme 2008; Lande 2015). For example, Davidson et al. (2011) proposed a meta-analysis that shows that invasive plant species exhibit a higher degree of phenotypic plasticity than closely related non-invasive species. In contrast, the number of studies on animal development strategies is still limited and strongly taxonomic biased towards the invertebrates (Fig. 8.2).

Box 8.1 Literature Survey
We conducted a literature search on Scopus for the terms (Plasticity) AND (Invasive OR alien OR invasion OR colonising OR invasiveness OR non-native) AND (development OR developmental OR growth) AND NOT (cancer) in titles, abstracts or keywords. The initial search yielded more than 1400 studies and after a refinement with subject area, source and keywords and a revision of the abstracts for the exclusion of all studies not referring to plants or animals, we reach 739 studies.

From the results of the inquiry, it emerges clearly that the interest in the study of developmental plasticity in the biological invasion process has grown much in recent years, going from less than 10 studies per year from 1983 until 2003 to 61 in 2020 (Fig. 8.1). The studies on plants are far more represented, being almost twice those on animal species. By looking at studies on animal taxa, a disproportion is well evident, with studies on insects and fish standing out for their number (Fig. 8.2).

Fostering our understanding of the traits that make an invader successful is necessary to improve our ability to manage invasions and their negative consequences for ecosystems (Mooney and Hobbs 2000). By relying on the available literature, we aim to address two main questions: (1) does developmental plasticity confer an adaptive advantage to alien animal species in the invasion process? (2) can early-life conditions in the origin environment prime individuals to be successful invaders?

8.2 The Good of Being Plastic

8.2.1 Introduction into a New Environment

Developmental plasticity may be advantageous when it allows a genotype to maintain or increase the Darwinian fitness across multiple environments (Bradshaw 1965; Baker 1974; Sultan 1987, 1995; Schlichting and Pigliucci 1998; Pigliucci 2001; Ghalambor et al. 2007). When the effective population size is small (which is usual in the early stages of an invasion process), adaptation by natural selection might take too long to occur, and alleles that have a selective advantage might even be lost by genetic drift (Wright 1931; Li 1978). However, plasticity enables organisms to adjust to the new conditions rapidly, even within a given generation, and the resulting phenotype may later become genetically encoded by 'genetic assimilation' (Baldwin 1896; Baker 1974; Robinson and Dukas 1999; Pigliucci 2001; Schlichting 2004; see Glossary). Thus, plasticity satisfies the crucial first step in adaptation to new environments, reducing the cost of directional selection and providing enough time for a population to become established (Pigliucci 2001; Ghalambor et al. 2007).

Thus, plasticity not only reduces the probability of extinction in new environments but also allows populations to move from one adaptive peak to another (Robinson and Dukas 1999; Pigliucci and Murren 2003; Price et al. 2003; West-Eberhard 2003; Schlichting 2004; Amarillo-Suarez and Fox 2006).

Developmental plasticity has been studied widely in plants (Fig. 8.1). Plants show dramatic effects on growth and development as a reaction to environmental conditions, and are also more easily cloned and grew in alternative environments than other organisms. Thus, much of our current knowledge on developmental plasticity comes from plant studies documenting the range of phenotypes that individual genotypes can produce in response to a wide range of environmental conditions (Sultan 2000). Richards et al. (2006) described three primary scenarios regarding the importance of developmental plasticity in plant invasions and the role of plasticity in maintaining fitness across different environments: (1) a Jack-of-all-trades situation, where through the plasticity of morphological or physiological traits, the invader is better able to maintain fitness in a variety of environments; (2) a Master-of-some situation, in which phenotypic plasticity allows the invader to take advantage of favourable environments; (3) a Jack-and-master that combines some of both of Jack-of-all-trades and of Master-of-some situations. Each scenario makes different predictions about the shape of the reaction norms (see Glossary) of invaders relative to that of the respective controls. Although this framework has been applied almost exclusively to plant species, it is possible to identify those same scenarios in invasions of animal species (Knop and Reusser 2012). The harlequin bug *Murgantia histrionica*, native to Central America, dispersed across most continental United States of America (Ludwig and Kok 1998; Zahn et al. 2008). In environments with lower temperatures, harlequin bugs develop into an adult phenotype with a higher percentage of dark colouration than individuals who have grown in warmer environments, thus maintaining the correct thermoregulation (Sibilia et al. 2018). This phenotypic response may be highly beneficial to harlequin bugs in colder environments, as darker-coloured individuals can subsequently engage in thermally dependent behaviours, such as feeding and reproduction (Sibilia et al. 2018). Temperature-associated traits and their plasticity can be influenced by developmental exposure to different thermal regimes (Bowler and Terblanche 2008), especially in ectothermic organisms that rely on ambient temperatures to modulate growth and metabolic rates (Beitinger et al. 2000; Ward et al. 2010; Rivera et al. 2021). Plasticity in thermal traits has been shown to improve the fitness of several invasive species, such as *Ceratitis capitata* (Mediterranean fruit fly) and *Ceratitis rosa* (Natal fruit fly) (Nyamukondiwa et al. 2013), the slug *Arion lusitanicus* (Donnelly et al. 2012), and species of collembolan springtails (*Pogonognathus* and *Isotomurus spp.*; Chown et al. 2007; Slabber et al. 2007), conferring the ability to spread in environments with different climatic conditions.

8.2.2 The New Biotic Environment

The establishment of a non-native species is determined by its ability to adapt not only to the abiotic characteristics of an invaded habitat, but also by its ability to cope with novel interspecific interactions (Dzialowski et al. 2003). Carry-over effects may be an important mechanism for invasive species experiencing new predatory or competitive environments (Garcia et al. 2017). Garcia et al. (2017) found morphological plasticity in American bullfrog (*Lithobates catesbeianus*) tadpoles exposed as embryos to different predation risk environments. In a high-risk scenario, bullfrog embryos exhibited a developmental carry-over response, hatching into larvae that grew 10% longer compared to individuals conditioned to lower risk environments. Although this developmental strategy entails a reduction in developmental rate and a longer time until metamorphosis, it increased both the swim and the escape performances. Thus, early life carry-over effects appear to improve the antipredator response of bullfrogs, potentially boosting invasion success.

There are also circumstances when, compared to local species, an invader species experiences less stringent allocation trade-offs. This is the case where the predation risk on invaders is low. The enemy release hypothesis (Keane and Crawley 2002) predicts that escape from co-evolved, specialist natural enemies (including parasites and pathogens) can facilitate the success of a species introduced into a novel area. Typically, alien species have fewer parasites and pathogens in the introduced range than in the native one (Müller-Schärer et al. 2004). Enemy escape should be accompanied by relaxed selection on defensive traits (Lahti et al. 2009). When those defensive traits are involved in trade-offs with other traits from an energetic point of view, a straightforward prediction is that enemy escape should allow the invasive species to allocate more metabolic resources to growth or reproduction (Mlynarek et al. 2017). For example, the Asian tiger mosquito (*Aedes albopictus*) shows a reduced infection load by its gut parasite *Ascogregarina taiwanensis* in the invaded site. As a consequence, they develop faster and attain sexual maturation earlier than the native mosquito *Ochlerotatus triseriatus* (Aliabadi and Juliano 2002). Studies on developmental plasticity in relation to different predation or competition pressures are, however, scarce. Experimental manipulations of these pressures would provide more direct evidence for the importance of developmental strategies for the invasiveness of a given species (Sakai et al. 2001). One relevant example lies with the red-eared slider turtle (*Trachemys scripta elegans*). This species is native to the Mississippi River Valley of the United States of America, with a broad distribution between Texas in the south and Illinois in the north (Ernst and Lovich 2009). The red-eared slider turtle is the most widespread invasive turtle species in the world, introduced mainly through pet trade in all continents but Antarctica. The introduction of the red-eared slider turtle had negative consequences for native turtle species: in Europe, it negatively impacts the European Pond turtles (*Emys orbicularis*) and the Spanish terrapin (*Mauremys leprosa*) through exploitative and interference competition (Cadi and Joly 2003, 2004; Polo-Cavia et al. 2009a, b, 2011). Pearson et al. (2015) found that red-eared slider turtles are better

competitors than the native red-bellied turtles (*Pseudemys rubriventris*), and such a superior competition capacity was linked to developmental strategy. They manipulated the intensity of competition of juveniles by altering turtle density and species composition in order to have low resource (higher density) and high resource (low density) scenarios. Under low food scenarios, red-eared slider turtles ingested more food, gained mass faster, and maintained body condition compared to red-bellied turtles, which exhibited a decline in body condition. When housed with conspecifics, red-eared slider turtles grew slower than when housed with mixed-species groups, suggesting that red-eared slider turtles rely on a fast developmental pace only when competing with other species (Pearson et al. 2015).

8.2.3 Plasticity in Traits Increasing Population Growth Rate

If the invasion propagule is able to survive to the conditions encountered in the new environment, the next step towards a self-sustaining population is reproduction and population growth (Blackburn et al. 2011). The reproductive rate can be increased by an increase in fecundity, an earlier age at first reproduction, a lengthening of the reproductive period, or a decrease in the peak reproductive age (Cole 1954; Lewontin 1965). Classically, successful colonisers are characterised by strategies that imply the ability to exploit the low density in the new environment during the expansion phases (Sakai et al. 2001). Kolar and Lodge (2001) have identified common features to successful colonisers in the different taxa r-selected life histories, including the use of the pioneer habitat, short generation time, high fertility, and high growth rate. Intriguingly, these life-history traits often differ between native populations and invasive populations within a single species (Phillips et al. 2010). In 1960s, the vendace (*Coregonus albula*) was translocated and introduced in Lake Inari, northern Finland, where it reached a high population density in the second half of the 1980s (Bøhn and Amundsen 1998). From the lake Inari, the species migrated downstream into the Pasvik River system where it was observed for the first time in 1988 (Amundsen et al. 1999). Substantial differences in life-history traits were observed by comparing the Lake Inari (source) and the downstream lake (colonist) populations. The colonist population consisted of small-sized individuals who reached maturity earlier in life than the source population, emphasising the importance of developmental strategies in increasing invasion success. Moreover, the annual mortality rates were much higher in the colonist than in the source population (Amundsen et al. 2012). Life-history theory predicts a trade-off in the allocation of resources among life-history traits because resources occur in limited supply, and traits compete for them (Stearns 1992). Relative to the source population, the colonist population displayed an r-selected strategy, characterised by a rapid life-history development, which came at a cost in terms of reduced longevity, a typical "live fast and die young" strategy (Amundsen et al. 2012). During the pioneer phase of introduction and establishment of invasion, with low density and interspecific competition, resource allocation in early reproduction and high fecundity can be

expected to trade-off with body size or survival (Davis 2005; Burton et al. 2010). In contrast, the source population may display more K-selected traits, such as higher age and body size at maturity and lower mortality, characteristics of later succession stages and saturated communities (Amundsen et al. 2012). Plasticity in the life-history strategy of a species is an important factor that contributes to determine the success of an invader (Rosecchi et al. 2001).

8.2.4 Plasticity in Traits Associated with Dispersal

Once a self-sustaining population is established, the last crucial stage of the invasion process is the spread (Phillips et al. 2010). Populations spread through a combination of demographic growth and dispersal. Developmental plasticity in dispersal traits may promote the continued spread of a newly established species beyond its point of introduction (Sakai et al. 2001). In insects, for example, the developmental temperature has strong effects on traits that govern dispersal, such as wing size and shape that influence the flight performance and the dispersal distance (Fraimout et al. 2018). The spotted-wing drosophila (*Drosophila suzukii*) is a particularly successful invader that has colonised more than 20 countries across Europe, South and North America in less than a decade. Native to Asia, the spotted-wing drosophila was introduced unintentionally through the transport of small fruits with which the species is closely associated. It is now considered one of the most important agricultural pest species throughout its invasive range. Given its remarkable plasticity in development, adult phenotypic traits and behaviour, this species successfully moved from unintentional introduction sites, becoming invasive in subtropical, temperate and boreal regions (Little et al. 2020). The exposure to different climatic conditions during developmental stages, eggs and larvae, confers to this species not only plasticity in development time and greater cold tolerance in adult flies, but also plasticity in wing shape and size. Fraimout et al. (2018) show that colder temperatures during development result in an adult with larger wings and narrower proximal sections, and a slightly broader wingtip, with consequences on flight performance. Cold reared spotted-wing drosophila could disperse faster and further compared with flies reared in warmer temperatures, potentially boosting the range expansion process in temperate and boreal regions (Little et al. 2020). In cane toads (*Rhinella marina*) some of the traits that made it one of the most successful invaders, as spontaneous activity and snout-urostyle length, are influenced by a mixture of genetic differences, environmental responses and genotype × environment interactions (Llewelyn et al. 2010; Stuart et al. 2019; Kelehear and Shine 2020). Moreover, Kelehear and Shine (2020) suggest a trade-off between dispersal and reproduction. Indeed, individuals at an expanding range edge exhibit enhancing dispersal traits, longer legs and narrower heads, but reduced reproductive investments (lower gonad mass).

8.3 Evolution of Plasticity During Invasion Process

Two main hypotheses have been proposed for the role of developmental plasticity in biological invasions. First, invasive species may be more plastic than non-invasive or native ones (Baker 1965; Marshall and Jain 1968; Williams et al. 1995; Durand and Goldstein 2001; McDowell 2002). Second, populations in the introduced range may evolve more remarkable plasticity than populations of the same species in the native range (Kaufman and Smouse 2001; Sexton et al. 2002; Parker et al. 2003). In fact, rapid evolutionary change appears to be common in invasive species (Brown and Marshall 1981; Thompson 1998; Mooney and Cleland 2001; Sakai et al. 2001; Lee 2002; Bossdorf et al. 2005), and rapid evolution of plasticity could play an essential role in explaining their success (Richards et al. 2006). Rohner and Moczek (2020) show that the dung beetles (*Onthophagus taurus*) rapidly evolved clinal population differentiation, and suggest that post-introduction evolution of developmental plasticity contributed to a significant degree to the successful invasion of North America by this species. Using a common garden rearing experiment, they tested four invasive populations collected along a latitudinal cline in the United States of America and one population from Italy, the ancestral range. The F1 offspring were raised in two temperature treatments that mimic local soil temperatures at a depth of 20 cm in the breeding season of the most southern (27 °C) and the most northern population (19 °C). They found a clinal variation in development time and body size that strongly depends on rearing temperature. This indicates that there was no genetic selection that decreased mean development time and body size. Instead, this phenotypic variation was the expression of thermal plasticity. Moreover, northern populations evolved reduced wing loading, which is predicted to yield enhanced lift at cool temperatures, and the clinal variation was more pronounced at cooler rearing temperatures, suggesting latitudinal differentiation in thermal plasticity.

8.4 Conclusion and Future Directions

Being plastic may reduce the extinction risk during the invasion process, since it allows individuals to develop phenotypes that best match the new environmental conditions, or that allow them to outcompete local species (Sultan 2000; Pfennig et al. 2010; Forsman 2015). During biological invasions, developmental plasticity may confer the ability to maintain fitness in a wide variety of environments, such as the case of the harlequin bug, allowing the invader to establish a reproductive population and to overcome the introduction stage. In the two successive stages of invasion (establishment and spread), population growth and dispersal determine the success of an invasive species (Phillips et al. 2010). The ability to modify the allocation of energy between reproductive and dispersal traits at the expense of traits that are not strictly related to fitness during the invasion, as in the case of traits

associated with defence from enemies, can make a successful invader (Phillips et al. 2010; Mlynarek et al. 2017). Developmental plasticity in life-history traits, as seen in the case of sand gobies, or in traits associated with dispersal, as the drosophila wing, increases the chances that a population of an alien species can grow and spread, thus becoming invasive.

Studies addressing the adaptive role of developmental plasticity in invasive species have mainly been focused on plants, thus we urge the need for more studies in other groups in order to best characterise the role of developmental plasticity in driving invasion processes. It will be important to compare populations from the invasive and the native range of the invasive species (home-and-away comparison), and populations of local species that might be affected by the invader, using for example common garden experiments (Richards et al. 2006). However, we also point out the importance of characterising the population invasion history, before investigating the evolution of plasticity relying on inter-population comparisons (Phillips et al. 2010). This is because developmental plasticity may decrease through genetic assimilation across time, which might hide any relevant environmentally-induced phenotypic variation (Pigliucci et al. 2006; West-Eberhard 2003). This point is well exemplified by the colonisation of different islands in Australia by island tiger snakes (*Notechis scutatus*). By comparing populations isolated on islands from less than 30 years ago to more than 9000 years ago exposed to selection for increased head size (i.e., ability to ingest large prey), it was shown that larger head size is achieved by plasticity in young populations, while in older populations it is achieved by genetic canalisation (Aubret and Shine 2009).

In conclusion, while we have emphasised the importance of developmental plasticity in biological invasions, the opposite is also true: the study of biological invasions has great potential to provide an excellent natural laboratory to investigate the adaptive meaning of development strategies and early-life experience. Identifying and analysing data on the role of developmental plasticity in the early stages of the invasion process will also enable us to highlight fundamental processes taking part in shaping local biodiversity patterns.

Glossary

Alien species species that are introduced, accidentally or intentionally, outside of their natural geographic range.

Invasive species they are plants, animals, pathogens and other organisms that are non-native to an ecosystem, and in which they spread triggering economic or environmental harms or adversely affecting human health.

Genetic assimilation it is a process whereby environmentally-induced phenotypic variation becomes constitutively produced (i.e., no longer requires the environmental signal for expression).

Reaction norm it is a graphical representation of the set of phenotypes that a single genotype produces in response to different environments or treatments; individuals show plasticity if their reaction norm is nonhorizontal.

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Chapter 9
Consequences of Developmental Exposure to Pollution: Importance of Stress-Coping Mechanisms

Frédéric Angelier

Abstract Environmental pollution is a global phenomenon that affects all continents and dozens of types of pollutants with highly different properties can be found on Earth. These pollutants may result in detrimental environmental conditions with clear negative effects on fitness, but they can also induce more pernicious and subtle effects by triggering maladaptive responses to environmental conditions. Importantly, the impact of pollutants on organismal systems is often also exacerbated during the developmental stage. Indeed, developmental conditions are known to affect the ontogeny of multiple integrative organismal systems, and notably the ontogeny of stress-coping mechanisms. These mechanisms involve cognition, the fight or flight response and the HPA axis; they are crucial to consider in the context of pollution because they govern the ability of the individual to adjust to the environmental perturbations that may arise from physical pollutants. In addition, they may also be disrupted by chemical pollutants, resulting in a maladaptive response to environmental conditions and in pathologies. In this chapter, we first provide an example of how developmental exposure to a chemical pollutant (lead, Pb) may disrupt stress-coping mechanisms with detrimental consequences later in life. Then, we illustrate the impact of physical pollutants on performance by focusing on the example of noise pollution. We especially aim to highlight the importance of stress-coping mechanisms and their flexibility in determining the ability of individuals to cope with noise pollution. Finally, we propose several avenues of research to better understand how wild species may adapt to this polluted world. We emphasize (1) the importance of considering the cumulative and interactive effects of physical and chemical pollutants on stress-coping mechanisms and performance; (2) the potential importance of priming hormesis in adjusting the functioning and the flexibility of stress-coping mechanisms to a polluted environment; (3) the need to consider microevolution to assess whether selection acts on stress-coping mechanisms and favors specific stress-coping traits that are beneficial in a polluted world.

F. Angelier (✉)
Centre d'Etudes Biologiques de Chizé, CNRS-La Rochelle Université, UMR 7372, Villiers en Bois, France
e-mail: frederic.angelier@cebc.cnrs.fr

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9.1 A Polluted World

9.1.1 Human Population Growth, Human Activities, and Global Pollution

Since the establishment of human societies, human activities have been associated with multiple types of pollution and notably with the release of multiple pollutants into the environment (Sauvé and Desrosiers 2014). This phenomenon increased to unprecedented rates during the industrial revolution (18th century) and it has accelerated since that period with the development of new technologies, energies, and agricultural processes (Vane et al. 2011; Hayes et al. 2017). Despite the development of several environmentally friendly policies, pollution is intrinsically and tightly linked to the social and economic needs of the worldwide human population. Therefore, it is expected that this coming century will be associated with an ongoing release of pollutants in the environment as the human population is expected to reach 11 billion by 2100 (Bradshaw and Brook 2014).

Importantly, environmental pollution is a global phenomenon that affects all continents and all ecosystems, although some geographical areas or biotopes are obviously affected to a greater extent than others (Wang et al. 2020). This global contamination mainly results from two concomitant factors. Firstly, humans have settled in all continents and human activities are virtually present everywhere on Earth, and even beyond with the recent multiplication of orbital space debris. Secondly, several pollutants can be transported from their area of emission to other areas through biotic (e.g., transfer of pollutants from one area to another through living organisms, Carbery et al. 2018) and abiotic processes (e.g., global atmospheric and ocean circulations, Zhang et al. 2019). For example, some pollutants have been found sometimes at very high concentrations in remote areas that were thought to be pristine (e.g., the Himalayas, or Polar areas, Wang et al. 2019). Initially, this pollution was restricted to specific locations, but the exponential growth of human populations, urban sprawl, the expansion of human activities to many habitats, and the global circulation of pollutants have led to a global contamination of Earth ecosystems (Bernhardt et al. 2017).

Historically, the detrimental effects of contaminants on non-target species have usually been discovered several years after their use and after the occurrence of specific health problems in humans or drastic population declines in wild species. The best example probably comes from DDT, which was used against mosquitoes worldwide. DDT appeared to affect the reproduction of birds by causing egg-thinning (Cooke 1973). The use of DDT has also been recognized as an important endocrine disruptor in humans, and it has been associated with developmental issues and with the occurrence of multiple pathologies in humans including cancer (reviewed in Hayes et al. 2017). Following these scientific studies and discoveries, strict regulations were set up and DDT was banned in most countries in the 70s. DDT is an excellent example of the delay that often exists between the

commercial use of a molecule and the gathering of robust data to assess the threat it may represent to human health and ecosystems (Sauvé and Desrosiers 2014).

Indeed, the exponential rise of the human population and the development of new technologies and industrial and agricultural processes is currently associated with the production and the release of hundreds of these so-called emerging pollutants into the environment (Sauvé and Desrosiers 2014). These molecules aim to replace older molecules that are no longer effective or that are associated with environmental and health concerns and so are progressively being banned by environmental and health agencies. It is now acknowledged that specific research efforts must be carried out to evaluate how humans and wildlife are exposed to these contaminants (the notion of "exposome," Karlsson et al. 2021), to understand their properties which lead to potential interactions with organisms (Pourchet et al. 2020), and to assess the health and environmental issues that are related to these emerging compounds (Dulio et al. 2018). Importantly, other factors may exacerbate current pollution and its effect on human health, so that it is now essential to study how other perturbations may affect the exposome and potentially exacerbate the impact of contaminants on biodiversity and humans (Karlsson et al. 2021). For example, it is predicted that climate change and heat waves will amplify the negative effects of the emission of air pollutants on human health in cities (Harlan and Ruddell 2011).

9.1.2 A Wide Variety of Pollutants

Because of the complexity and multiple sources of pollution, it would understandably be unrealistic to draw up a comprehensive description of this polluted world. Two wide types of pollutants can however be described: (1) chemical pollutants, which include the release of specific compounds or particles in the environment. These pollutants can be transferred to the environment and can contaminate wild organisms through ingestion, inhalation or cutaneous exposure with associated potential health issues. These pollutants are those focused on earlier in this chapter. They include numerous molecules that are used by humans for multiple activities and that have been released in the environment, sometimes for decades. The most ubiquitous of these organic pollutants belong to the following classes: polychlorinated biphenyls, halogenated hydrocarbons, estrogen analogues, phthalates, dioxins, perfluorinated compounds, and brominated flame retardants (Manzetti et al. 2014). Chemical pollutants also include inorganic molecules (i.e., trace elements) that are naturally present in the environment and are even necessary to allow most living organisms to function (e.g., Fe, Cu, Zn). Human activities are, however, associated with important releases of these trace elements and their environmental concentrations may then reach an upper threshold that is associated with significant toxicological effects. Other trace elements have key detrimental effects on living organisms, even at very low environmental doses (e.g., Pb, Cd, As). Importantly, these inorganic pollutants are persistent in the environment and are not

bio-degradable. This wide variety of inorganic and organic molecules is associated with different chemical and biological properties (e.g., half-life, toxicity, bioaccumulation and biotransformation potentials) that determine the toxicological threat that they represent for the environment and human health; (2) non-chemical or physical pollutants, which are associated with the modification of an individual's environment and with an alteration of environmental cues (Halfwerk and Slabbekoorn 2015). This pollution includes, for example, noise pollution, light pollution or electromagnetic pollution which are all known to create unreliable environmental cues that affect wildlife (Dominoni et al. 2020a, b), and to be associated with health issues in humans (e.g., Goines and Hagler 2007). As for chemical pollution, this physical pollution is complex because it is diverse in nature and intensity and it depends on the emitting sources of pollution. For example, noise and light pollution can vary according to the frequency (noise, Slabbekoorn 2019) or the spectrum (light, Gaston et al. 2012), the intensity, and the duration of the pollution. Indeed, the characteristics of physical pollutants are important determinants on their impact on the physiology and the behavior of vertebrates. For example, recent studies have suggested that the intensity and the spectrum of light can modulate the impact of light pollution on circadian rhythms of wild birds (Ulgezen et al. 2019).

9.1.3 How Can Pollutants Affect Vertebrates?

Historically, toxicological studies have focused on the detrimental effects that chemical and physical pollutants can have on the performance of vertebrates. These studies have aimed to link these pollutants with the occurrence of morbid pathologies in humans (cardiovascular diseases, metabolic syndromes, cancer, neurodegenerative diseases, psychological disorders, e.g., Turner et al. 2017) and they have relied on large-scale epidemiological surveys or on toxicological laboratory experiments in animal models (e.g., Zou et al. 2009). Similarly, ecological and ecotoxicological studies have intended to determine the impact of these pollutants on wild vertebrates (Saaristo et al. 2018). Although experimental ecological studies are very rare for ethical and logistical reasons, correlative studies have demonstrated that some legacy or emerging chemical pollutants are associated with reduced survival or reproductive performance (e.g., Goutte et al. 2014, 2018; Sebastiano et al. 2020). Regarding physical pollutants, such as noise or light pollution, epidemiological studies and laboratory experiments have demonstrated that these pollutants can also be associated with pathologies in humans (sleep disorders, cardiovascular diseases, psychological disorders, retinal degeneration, Contín et al. 2016), and field studies on wild vertebrates have also demonstrated that noise and light pollution can alter the reproductive performance of animals and induce disorders that could be associated with reduced longevity (e.g., sleep disorders, oxidative stress; e.g., Ouyang et al. 2017; Dominoni and Nelson 2018). Beyond these strong effects of pollutants on the health of humans and wild vertebrates, pollutants can also

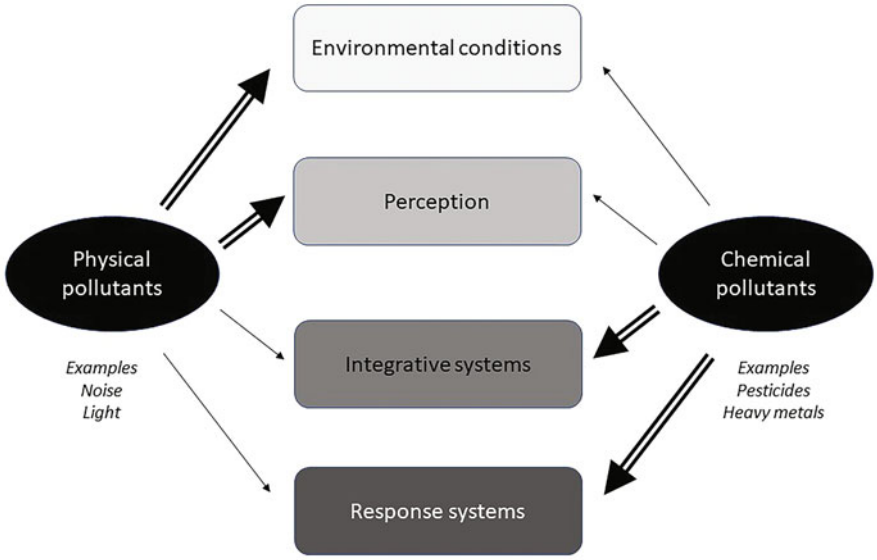

Fig. 9.1 Theoretical influence of chemical and physical pollutants on the functioning of vertebrates. Chemical pollutants are expected to have a strong impact on integrative and response systems through a direct disruption of key central organismal systems ("organismal disrupting pollutant"). Physical pollutants are expected to have a strong impact on environmental conditions and on the perception of the environment ("sensory pollutant," Halfwerk and Slabbekoorn 2015). Chemical pollutants could also affect the environment itself and could also affect sensory systems. Similarly, physical pollutants can also affect the organismal systems (integrative and response systems) through indirect effects (phenotypic plasticity and environmentally driven physiological and neurobiological changes)

have more subtle and pernicious effects. The rest of this chapter will focus on these sublethal effects and will specifically endeavor to evaluate how they can affect the ability of individuals to fulfill their seasonal and life cycles in a polluted environment.

Several modes of actions of pollutants may result in reduced performance in wild vertebrates. Firstly, pollutants may well of course affect the environment itself and result in detrimental environmental conditions. These conditions will subsequently constrain the individuals in terms of resources and they will therefore lead to poor performance during some or even all life-history stages (Fig. 9.1). For example, the release of systemic insecticides in agroecosystems may drastically reduce the quantity of insects in the environment (Cardoso et al. 2020), leading to reduced food abundance for all the insectivorous species, and therefore to poor reproductive and survival performance (Stanton et al. 2018). By drastically affecting environmental conditions, pollutants may also induce maladaptive responses, especially if the pollutants induce environmental conditions that are not within the range of environmental conditions the species has been selected for (Sih et al. 2011). For example, artificial light at night may totally disrupt circadian rhythms and lead to reproduction

impairment in some vertebrates, as recently demonstrated in the Australian budgerigar, *Melopsittacus undulatus* (Malek and Haim 2019). Secondly, pollutants may also induce more pernicious and subtle effects by triggering maladaptive responses to environmental conditions that are within the range of environmental conditions the species has been selected for (Fig. 9.1). Specifically, pollutants could affect the different steps that govern the individual response to environmental cues: (1) the perception of the environmental conditions; (2) the processing of the information by integrative systems; (3) the organismal response to the environmental cues. Classically, chemical pollutants are known to disrupt central organismal systems (Crisp et al. 1998). In the context of these subtle non-lethal effects, they are therefore likely to affect the processing of the information and the organismal response to the environment through their impact on integrative systems (brain and neurological effects, endocrine disruption). They can also affect the environment itself, notably if these chemical pollutants have an effect on other compartments of the ecosystem (e.g., food abundance). The impact of physical pollutants on wild vertebrates is more likely to be mediated through a direct modification of the environment (e.g., noise or light) and through an effect on the perception of the environmental conditions (indeed they are often called "sensory pollutants," Halfwerk and Slabbekoorn 2015; Dominoni et al. 2020a, b). Physical pollutants may also indirectly affect the functioning of the integrative and response systems through phenotypic adjustments, particularly if they occur during the ontogenetic phases of these systems.

9.1.4 Importance of the Developmental Period

In this context, specific attention should be paid to the developmental stage because the ontogeny of multiple integrative organismal systems is mainly determined during this stage (Minelli 2003). As explained earlier, these systems are crucial to process the perceived information and to proceed with a phenotypic response. During development, the plasticity of all these systems is set up and developmental conditions orientate these systems toward a specific function that can usually only be modified to a limited extent during the post-developmental period (de Graaf-Peters and Hadders-Algra 2006). For example, brain structures are mainly determined during the prenatal and postnatal developmental periods. Brain development is under control of gene expression during that period, but prenatal and postnatal environmental conditions also play a crucial role in brain development because they establish and refine neural organization in specific ways that aim to adjust the structure and the functioning of the brain to the conditions in which the organism will live (reviewed in Stiles and Jernigan 2010). Therefore, developmental conditions may have a strong incidence on the ability of individuals to cope with pollutants, or more generally with perturbations, later in life.

In addition, the impact of pollutants on organismal systems is often also exacerbated during the developmental stage. For example, brain development is very vulnerable to pollutants in early life compared to later stages of life (Grandjean

and Landrigan 2014). Indeed, previous experiments have shown that urban air pollution and fine particles result in altered brain development during the prenatal and postnatal periods and this was associated with cognitive issues, reduced neurogenesis and neuropathologies in mice (Allen et al. 2014; Sunyer and Dadvand 2019; Patten et al. 2020). Because of this sensitivity, strict regulations are set up for pregnant women and children in humans, especially regarding the exposure to chemical pollutants. This suggests that the impact of pollutants on the development of key integrative systems may then represent a lifetime burden for the organism with permanent detrimental effects.

9.2 The Relevance to Focus on Stress-Coping Mechanisms in the Context of Pollution

When focusing on the impact of pollutants on wildlife, it is undoubtedly crucial to focus on stress-coping mechanisms because (1) they are required to adjust to the environmental perturbations that may arise from physical pollutants (e.g., noise or light pollution); (2) they may be disrupted by chemical pollutants, resulting in a maladaptive response to environmental conditions and in pathologies. However, surprisingly, stress-coping behavioral and physiological mechanisms have been relatively overlooked in comparison with other organismal systems and endocrine axes.

9.2.1 Stress-Coping Mechanisms: From Behavior to Endocrine Mechanisms

When individuals encounter and/or perceive challenging environmental conditions, a suite of behavioral and physiological changes are activated to allow the organism to maintain a homeostatic state (i.e., the concept of allostasis, McEwen and Wingfield 2003; Romero et al. 2000). These behavioral and physiological responses to perturbations have often been used to define specific coping styles (proactive vs. reactive, Koolhaas et al. 1999). Firstly, this stress response involves the immediate behavioral fight or flight response, which is associated with the sympathetic branch of the autonomic nervous system and the release of catecholamines (Wingfield 2003). This response is typically associated with a rapid increase of heart and respiratory rates, and a vasodilatation of the vessels that supply oxygen to the organs necessary to cope with the stressor (e.g., muscle). It is also associated with the vasoconstriction of the vessels that supply oxygen to facultative functions (not necessary for immediate survival, e.g., digestive organs), and with a rapid conversion of glycogen to glucose to supply the brain and the muscles with energy (McCarty 2016a, b). This response mainly translates into contrasted coping

behavioral strategies (e.g., propensity to adopt an escape behavior). Secondly, this stress response also involves the Hypothalamus-Pituitary-Adrenal (HPA) axis and the regulation of circulating glucocorticoid levels (cortisol or corticosterone, Wingfield 2013). Increased circulating levels of these hormones will in turn modulate the functioning of several organismal systems, such as immunity, metabolism, and reproduction. It will therefore redirect resources from specific functions (e.g., reproduction) toward functions that are essential to immediate survival (Sapolsky et al. 2000). This physiological stress response is thought to prepare the organism to cope with the stressor in case it persists for an extended period of time (the preparative hypothesis, Romero 2002). Importantly, the physiological stress systems also involve the termination of the stress response that allows the organism to avoid the detrimental effect of chronic stress (e.g., Zimmer et al. 2019). Overall, the fight or flight response plays an important role in mobilizing immediate adaptive resources of the body, and the HPA stress response provides for more enduring adjustments to prolonged stress (Frankenhaeuser 1986). Another important way to cope with stress is the development of cognitive processes that are linked to learning and memory (the cognitive buffer hypothesis, Sol 2009). Firstly, learning and memory may help individuals to avoid stressful situations by adjusting their behavior or their physiology. Secondly, they may also help individuals to elicit a stress response that is well adjusted to the stressful situation, and which optimize its benefits (Ursin and Eriksen 2004).

9.2.2 Stress-Coping Mechanisms: The Target of Pollutants

In the context of a polluted world that can affect the life cycle and the seasonal routines of organisms, it is logical to specifically study these mechanisms (Jacobs and Wingfield 2000). They can be the target of the pollutants themselves: pollutants may alter the functioning of these stress-coping mechanisms, leading therefore to maladapted responses to specific environmental conditions (Wingfield and Mukai 2009). This is typically the case for chemical pollutants that disrupt the functioning of physiological systems (e.g., endocrine disruptor chemicals). Indeed, there is increasing evidence that many pollutants can have sublethal effects on vertebrates and can disrupt endocrine and neurological functions, including the HPA axis and the autonomic nervous system (Harvey 2016; Yaglova et al. 2017; Di Lorenzo et al. 2020). In addition, pollutants also seem to detrimentally affect cognition and the development of the brain, therefore impairing learning and memory in humans (Sunyer et al. 2015; Clifford et al. 2016) and wildlife (Jacquin et al. 2020) with potential consequences on their ability to cope with stressors (the cognitive buffer hypothesis, Sol 2009). All these disruptions may impact the stress response in its globality (fight or flight response, HPA axis, and cognition) with potential important fitness costs for wild vertebrates (reduced survival and reduced reproductive performance), and serious pathologies for humans.

9.2.3 *Stress-Coping Mechanisms: How to Adjust to a Polluted Habitat*

Stress-coping mechanisms will determine the response of the organism to the environmental changes that will be associated with the pollutants. As detailed earlier, pollutants may affect not only the functioning of the stress-coping mechanisms (see Sect. 9.1.3), but also the environment or the perception of the environment by individuals (Halfwerk and Slabbekoorn 2015; Dominoni et al. 2020a, b). Poor environmental conditions will activate the stress-coping mechanisms and will lead to phenotypic responses that will be associated with fitness costs and benefits (Wingfield et al. 1998; Wingfield 2013). This stress response aims to help the organism cope with the stressor and it should theoretically allow the organism to cope with the pollutant (Wingfield et al. 1998; Angelier and Wingfield 2013; Schoenle et al. 2018). Individuals may appropriately cope with their new polluted habitat by adopting fresh life-history strategies and by learning how to avoid or cope with the new environmental conditions. The pollutants may, however, induce environmental changes that are incompatible with the requirements of the individual even when the stress response is activated (Angelier and Wingfield 2013). In that scenario, the stress response may lead to the dispersal and the colonization of an alternative habitat (unpolluted). If such dispersal is not possible (there is no appropriate habitat within the dispersal range of the individual), the ineffective stress response will result in null fitness (so no reproduction before death, Fig. 9.2).

When the pollutant affects the perception of the environment, it may lead to inappropriate environmental cues (Halfwerk and Slabbekoorn 2015). In this case, there might be a mismatch between the stress response and the actual environmental conditions, thus the degree of activation of the stress-coping mechanisms will be inappropriate to cope with the actual environmental conditions (Fig. 9.2). As extensively reviewed by Dominoni et al. (2020a, b), these inappropriate environmental cues may result from masking effects of pollutants. In terms of stress response, this inappropriate perception of the environmental situation will translate into a heightened or dampened stress response relative to the optimal stress response. Because the stress response is associated with fitness costs and benefits, this mismatch will respectively increase and decrease these fitness costs and benefits and will jeopardize the persistence of the individual in this polluted habitat (Angelier and Wingfield 2013).

9.2.4 *Flexibility of Stress-Coping Mechanisms: Importance of the Developmental Period*

These stress-coping mechanisms and coping styles are often tightly linked to individual performance and fitness in wild vertebrates. They are indeed thought to mediate life-history trade-offs, and as a consequence, to govern the decisions that

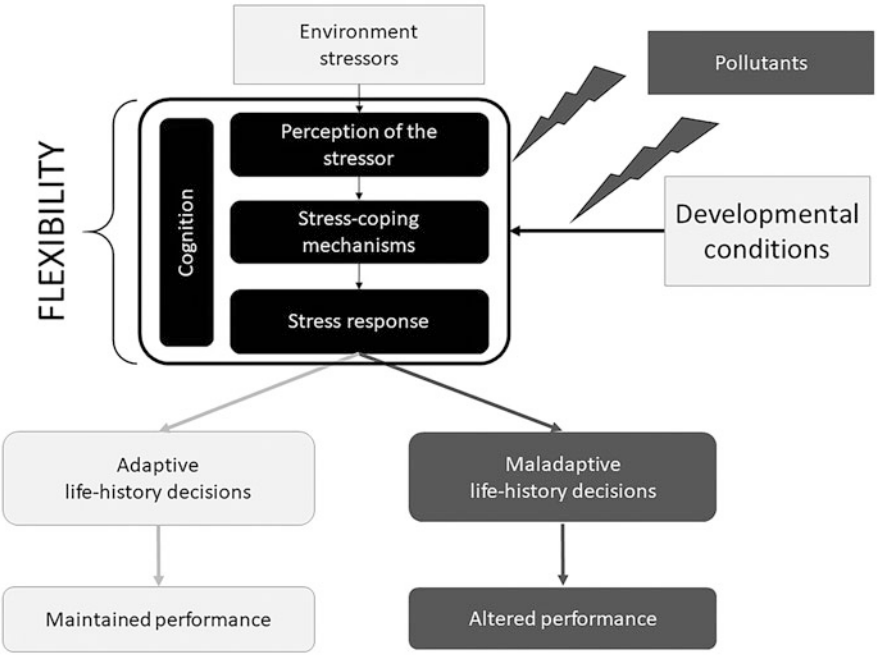

Fig. 9.2 Impact of pollutants on the ability of individuals to adjust the functioning of their stress-coping mechanisms to the environment. Pollutants may primarily disrupt the functioning of these mechanisms by altering their ontogeny during the developmental period, although they can also disrupt them during adulthood. This disruption may reduce the flexibility of these adaptive stress-coping mechanisms and/or may lead to maladaptive responses to environmental stressors with maladaptive life-history decisions, altered performance, and reduced fitness

individuals will adopt when facing specific environmental conditions (Angelier and Wingfield 2013; Taff and Vitousek 2016). In that respect, their study appears relevant to assess whether pollutants lead to maladaptive life-history strategies through their alteration. Importantly, most of these stress-coping mechanisms are heritable and at least partly repeatable, suggesting that they can be under selection and may play a key role in the ability of species to persist in polluted environments. Despite this heritability, these mechanisms are still flexible to some extent and it has been convincingly demonstrated that individuals are able to modulate their stress responses according to their individual state and the environmental conditions they encounter (Wingfield and Sapolsky 2003; Taff and Vitousek 2016). Importantly, this flexibility is certainly crucial in the context of a polluted world because the ability of individuals to adjust their stress response to a wide range of environmental conditions may allow them to complete their life cycle despite the pollution (Saaristo et al. 2018).

The flexibility of these mechanisms is certainly genetically determined and under selection (Hau et al. 2016), but importantly, there is also very strong evidence that prenatal and postnatal developmental conditions can have a strong impact on the

ontogeny of these systems and on their flexibility later in life (Taff and Vitousek 2016). During the developmental period, the ontogeny of multiple systems—including neurological pathways and endocrine axis—is indeed modulated by variations in hormonal levels (Groothuis and Schwabl 2008). For example, there is strong evidence that glucocorticoids are important mediators of ontogenetic transitions in vertebrates and that exposure to glucocorticoids during the developmental period can have important long-lasting effects on the phenotype and life-history strategies (Wada 2008; Marasco et al. 2012; Hau et al. 2016; Dupont et al. 2019). This means that pollutants, as endocrine disruptors, may affect the exposure of the embryo or the offspring to hormones with a potentially strong impact on the ontogeny of these systems, and possibly on their functioning and flexibility later in life (Fig. 9.2). This impact could be mediated by the occurrence of physical and chemical pollutants that alter daily and seasonal endocrine cycles, but also by chemical endocrine disruptors that may affect the degree of exposure of the developing organism to specific hormones (Fig. 9.2).

9.3 Influence of Chemical Pollutants on Stress-Coping Mechanisms: The Example of Lead (Pb)

The Anthropocene is associated with a large panel of anthropogenic activities and the related release of chemical pollutants in the environment. This paragraph aims to illustrate the potential disrupting effects of such pollutants on stress-coping mechanisms by focusing on the historical example of lead (Pb), a well-studied pollutant that is of primary concern for humans, wildlife, and the environment (Levin et al. 2021).

9.3.1 Developmental Impact of Exposure to Lead on Stress-Coping Mechanisms

A large number of studies have focused on the impact of lead exposure on the development of organismal functions (Fig. 9.3a), mainly because lead has been a major concern in child development for decades (Shefa and Héroux 2017). As a result, a great deal of data come from epidemiological studies on human populations. For example, studies of cohorts of children have convincingly shown that lead exposure during development is associated with cognitive disorders (e.g., Kim et al. 2013), increased cortisol secretion in response to stress (e.g., Gump et al. 2008), increased blood pressure (Zhang et al. 2012), and altered brain structure (Marshall et al. 2020).

In animal models, developmental exposure to lead has been associated with the development of cardiovascular issues, such as hypertension (Shvachiy et al. 2020;

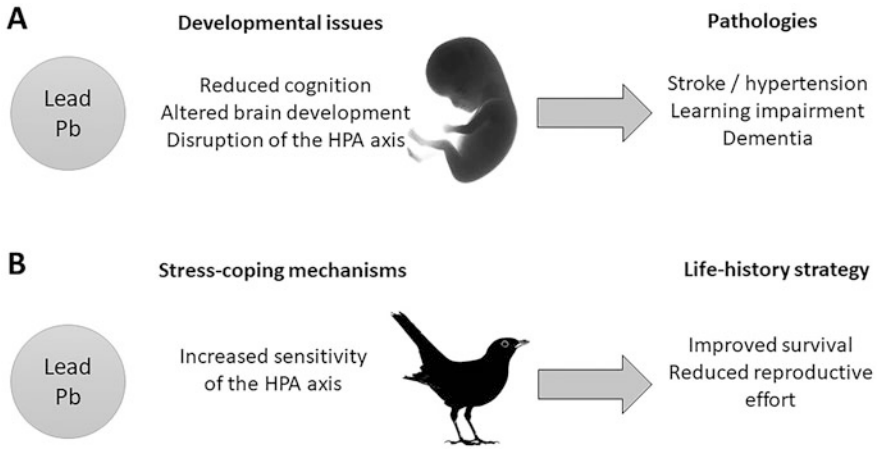

Fig. 9.3 Impact of lead on vertebrates. (**a**) Biomedical studies have demonstrated that developmental exposure to lead is associated with the alteration of the ontogeny of several stress-coping mechanisms, including brain development and the HPA endocrine axis. Such disruption is associated with the occurrence of multiple pathologies in children and adults. (**b**) Ecotoxicological studies have reported that lead contamination is associated with a disruption of the HPA axis and with an increased sensitivity of this endocrine axis to stressors. This modification has been related to a reduced reproductive investment, and as a result to an increased survival in some wild birds. This suggests that exposure to lead may alter life-history strategies in wild vertebrates

Chen et al. 2021). Little data is, however, available on the impact of lead exposure on the sympathetic branch of the autonomic nervous system and the release of catecholamines because most studies have focused on cardiovascular pathologies rather than the fight or flight stress response itself. However, in humans, exposure to lead results in increased heart rate and arterial pressure (Lai et al. 2002), and this could be mediated by a direct effect of lead on the secretion of catecholamines (Carmignani et al. 2000). In addition, developmental lead exposure was associated with a reduced escape behavior in zebrafish larvae, suggesting that lead may affect the fight or flight response (Rice et al. 2011).

Developmental exposure to lead has been reported to have strong effects on several endocrine mechanisms (Doumouchtsis et al. 2009), including the HPA axis. In animal models, exposure to lead results in an increased secretion of cortisol levels (HPA axis) in developing rats (Vyskočil et al. 1990). Importantly, exposure to lead can affect several components of the HPA axis. For example, lead seems to affect not only the secretion of glucocorticoids by the adrenals, but also the glucocorticoid receptors binding (Sobolewski et al. 2018), and the negative feedback system (Rossi-George et al. 2009). Exposure to lead during the developmental period has permanent effects on the HPA axis even when individuals are no longer exposed to lead after the developmental period (Cory-Slechta et al. 2004), and this can lead to psychosocial pathologies (Haider et al. 2013). More specifically, in rats, exposure to lead during the prenatal period results in a modified stress response later in life (Virgolini et al. 2008), suggesting that exposure to lead might disrupt this

stress-coping mechanism and potentially lead to maladaptive behavioral and physiological stress responses (Rossi-George et al. 2011).

Prenatal or postnatal exposure to lead has also been associated with a permanent reduction of memory (Shvachiy et al. 2020) and with learning and cognitive impairments in rats and mice (Rodrigues et al. 1996; Kuhlmann et al. 1997; Morgan et al. 2001). Experimental studies have shown that lead has a strong toxic effect on the development of the brain during the prenatal and the postnatal stages (Toscano and Guilarte 2005; Verstraeten et al. 2008), notably by inducing cell apoptosis in the brain and by resulting in a reduced number of cognition-related proteins (Hossain et al. 2016). Interestingly, similar effects have been found in animal fish and bird models and developmental exposure to lead has been experimentally shown to alter brain structures and to induce cognitive deficit and learning impairments (Xu et al. 2016; Goodchild et al. 2021).

Overall, these studies clearly demonstrate that developmental exposure to lead can affect a wide range of stress-coping mechanisms. Because these epidemiological and biomedical studies aim primarily to understand the pathologies that are linked to developmental exposure to lead, they do not necessarily allow us to assess how exposure to lead may disrupt the ability of individuals to cope with environmental daily and seasonal challenges (Fig. 9.3a). However, they provide crucial information to reliably test how lead functionally affects stress-coping mechanisms, and therefore to understand its potential impact on the ability of organisms to adapt to a changing world.

9.3.2 Wildlife, Exposure to Lead, and Fitness Consequences?

In the wild, several studies have reported that vertebrates can be exposed and contaminated by lead. Such contamination usually occurs because vertebrates exploit some habitats that are polluted by current or past human activities, such as industrial sites (e.g., Scheifler et al. 2006; Fritsch et al. 2012), urbanized areas (e.g., Bichet et al. 2013; Orłowski et al. 2014), or landfills (e.g., de la Casa-Resino et al. 2014). Most data come from urban ecotoxicological studies because cities are characterized by a global lead contamination of the environment, the animals and the humans (Levin et al. 2021). In bird species, lead seems to accumulate in the renal area, the liver, and the brain (Torimoto et al. 2021), suggesting that it may have important effects on cognition (brain) and glucocorticoid regulation by the adrenal glands. Because of the difficulty in studying cognition, the fight or flight response and the release of catecholamines in wild animals, no data is to our knowledge available regarding these stress-coping mechanisms in wild vertebrates (but see Grunst et al. 2020 for problem solving tasks). However, a few studies have examined the impact of lead contamination on the HPA axis of wild birds (Chatelain et al. 2018). In white storks, Baos et al. (2006) found that blood lead levels were positively correlated with stress-induced corticosterone levels (but not baseline corticosterone levels), suggesting that lead may increase the secretion of glucocorticoids in

response to stressors (Fig. 9.3b). Supporting this result further, Meillère et al. (2016) found that in blackbirds feather lead levels were positively correlated with feather corticosterone levels, a proxy of stress-induced corticosterone levels in birds (Bortolotti et al. 2008).

Although the impact of lead on survival has rarely been assessed in wild vertebrates, several studies have suggested that lead and other trace elements may impair reproductive performance (Janssens et al. 2003; Eeva et al. 2009, but see Eeva et al. 2014), even at a rather low level of contamination (Chatelain et al. 2021). Interestingly, two recent correlative studies support the idea that the disruption of stress-coping mechanisms by lead may result in drastic changes in life-history strategies (Guo et al. 2018; Fritsch et al. 2019; Fig. 9.3b). Further supporting this idea, another recent study of an urban songbird found that exposure to lead was clearly associated with a change in territoriality and aggressive behavior, two variables that are tightly linked to life-history strategy (McClelland et al. 2019). In blackbirds, blood lead levels were associated with increased longevity, but with reduced reproductive performance. Overall, lead contamination resulted in reduced lifetime reproductive success in that species (Fritsch et al. 2019). Due to the lack of experimental data, strong evidence is required to conclude that exposure to lead may induce maladaptive stress-coping strategies with detrimental fitness consequences. However, this correlational field data suggests that exposure to lead may lead to maladaptive stress-coping strategies and reduced fitness (Fritsch et al. 2019) through its disrupting effect on major stress endocrine axes (e.g., Baos et al. 2006; Meillère et al. 2016). Future studies should experimentally test whether exposure to lead affects life-history strategies and lifetime reproductive success through changes in the functioning of stress-coping mechanisms, such as the regulation of glucocorticoids (Eeva et al. 2006).

9.4 Influence of Physical Pollutants on Stress-Coping Mechanisms: The Example of Noise Pollution

In addition to the release of chemical pollutants in the environment, human activities are also associated with other types of pollutants, such as light and noise pollution. Here, the intention is to illustrate the impact of such pollutants on performance by focusing specifically on the example of noise pollution, a physical pollutant of global concern for human health and wildlife (Goines and Hagler 2007; Slabbekoorn 2019). We also aim to highlight the importance of stress-coping mechanisms in determining the ability of individuals to cope with such pollutants.

9.4.1 What Are the Effects of Noise Pollution on Performance?

In humans, there is evidence that noise pollution is associated with pathologies, often it seems related to chronic stress. For example, noise pollution has been associated with sleep disorders, more specifically reduced sleep duration and fragmented sleep (reviewed in Halperin 2014). In addition, noise pollution can increase blood pressure, lead to hypertension, and result in a higher risk of cardiovascular failure and stroke (reviewed in Stansfeld and Matheson 2003; Münzel and Daiber 2018). All these health concerns are intrinsically linked to stress regulation because of the clear interconnection between sleep, cardiovascular pathologies, and chronic stress. Indeed, noise pollution activates stress-coping mechanisms and is associated with the release of catecholamines (Borrell et al. 1980) and glucocorticoids (reviewed in Münzel et al. 2021). Animal studies have supported this idea that chronic stress could mediate the detrimental effect of noise pollution on health. They have shown that exposure to noise alters metabolism and impairs immunity and reproduction (Kight and Swaddle 2011), three systems that are functionally related to chronic stress (Dickens and Romero 2013).

Noise pollution is also linked to cognitive deficits in humans and laboratory animals. For example, noise pollution has been associated with learning impairments and reduced memory abilities (Stansfeld and Matheson 2003), and with the development of cognitive pathologies in old age (e.g., dementia, Paul et al. 2019). These effects seem to be at least partly mediated by a direct impact of noise on some brain structures (e.g., hippocampus) that could be linked to stress (Cheng et al. 2011). Indeed, cognition is functionally linked to stress (Lupien et al. 2007; Sandi 2013), and there is increasing evidence that cognitive impairments may be mediated by an effect of noise pollution on stress-coping mechanisms (Jafari et al. 2020). In wild animals, noise pollution has been shown to induce a state of chronic stress in multiple species with reduced body condition, and elevated circulating levels of glucocorticoids (e.g., Tennessen et al. 2014; Kleist et al. 2018; Zollinger et al. 2019; Mills et al. 2020). Importantly, experimental studies have demonstrated that noise pollution can impair memory and spatial learning (Osbrink et al. 2021), reproduction, and survival (Schroeder et al. 2012; Blickley et al. 2012; Kight and Swaddle 2011; Halfwerk and Slabbekoorn 2013; de Jong et al. 2020), further emphasizing the detrimental impact of noise pollution on performance.

Importantly, all these detrimental effects of noise pollution on health seem exacerbated during the developmental period (Gupta et al. 2018). For example, epidemiological studies have suggested that noise pollution impairs cognitive development with non-reversible effects in children (Stansfeld et al. 2005; Klatte et al. 2013). Experimental studies have also shown that exposure to noise during development affects neurogenesis and the ontogeny of spatial memory (Kim et al. 2006). In developing wild animals, noise pollution often translates in altered growth, high oxidative damages, and elevated levels of glucocorticoids through direct effects on the developing individuals (e.g., Meillère et al. 2015a; Raap et al. 2017; Injaian et al.

2018a, b), although these effects may also be partly mediated by indirect effects on parental behavior and parental foraging efficiency (e.g., Luo et al. 2015; Meillère et al. 2015b; Nedelec et al. 2017). Our current knowledge of the long-term consequences of developmental exposure to noise pollution remains limited because of the lack of experimental and correlational data (Stansfeld and Clark 2015). However, noise exposure seems to translate into developmental stress (e.g., elevated levels of glucocorticoids), and it is well-known that such stress has detrimental long-lasting consequences on multiple physiological and behavioral systems (Welberg and Seckl 2001; Cottrell 2009; Spencer 2017).

9.4.2 Importance of Stress-Coping Mechanisms to Adjust to Noise Pollution

Noise pollution is intrinsically linked to stress-coping mechanisms because sounds are used by vertebrates to assess their environment and any potential stressor. Indeed, the auditory system is functionally connected to stress-coping integrative systems, such as the autonomic nervous and the neuroendocrine systems, which govern the fight or flight response and the HPA system (Westman and Walters 1981). Because the activation of stress-coping mechanisms is not only associated with fitness benefits, but also fitness costs (Wingfield 2003, 2013), their degree of activation must be appropriate and adjusted to the environmental situation in order to optimize organismal fitness (Wingfield and Sapolsky 2003; Angelier and Wingfield 2013). In that sense, noise pollution can represent an important challenge because it can alter the direction or the intensity of the link that exists between the perceived environmental conditions and the threat that they actually represent (the concept of "sensory pollution," Halfwerk and Slabbekoorn 2015). For example, in most species, noise pollution may represent a stressful situation either because it produces sounds of high intensity that are perceived as stressors themselves (known as misleading effects, Dominoni et al. 2020a, b) or because it can create a background noise that reduces the ability of the individual to perceive or detect some potential threats (masking or distracting effects, Dominoni et al. 2020a, b). Overall, noise pollution is expected to trigger an activation of stress-coping mechanisms. If these mechanisms are associated with dispersal, the organism will be able to escape the noisy area and will resume its normal daily and seasonal routine. This strategy will, however, be associated with some costs because the organism will have left an environment that appeared, but was not, in fact, detrimental. If these mechanisms do not activate dispersal or if dispersal is not an option (either because the organism has a limited dispersal capacity or because noise pollution is general), their activation will not help to cope with the perceived stressful situation (i.e., noise pollution) and it will lead to a state of chronic stress. This state of chronic stress will in turn lead to poor performance and to pathologies, as described earlier.

To cope with such pollution, individuals need to adjust the functioning of these stress-coping mechanisms to the noisy environment. In other words, the degree of activation of these mechanisms needs to be modulated according to the costs and benefits they provide to the organism (Angelier and Wingfield 2013). In this context, the flexibility of these mechanisms—habituation and sensitization—is certainly a key variable to consider when focusing on the ability to adjust to stressors in general, and noise pollution in particular (Radley et al. 2015; Blumstein 2016). There is indeed evidence that such flexibility is present in animals. For example, repeated experimental exposure to noise was associated with a progressive reduction of the catecholamine and corticosterone stress response in adult rats (de Boer et al. 1988). Similarly, fish reduce their behavioral stress response when exposed to repeated noise stress (Neo et al. 2018). This flexibility may even predict the ability of species to cope with a noisy environment or not (Lowry et al. 2013; Møller 2013). For example, urban birds have been shown to habituate to human disturbance and noise, and as a result, to dampen their behavioral stress response in cities (reduced flight initiation distance, Blumstein 2013). However, flexibility also seems limited under some circumstances, and this may limit the ability of the organism to adjust to noise pollution. For example, recent studies have found that the activation of stress-coping mechanisms are not necessarily modulated according to repeated exposure to noise pollution in adult wild animals (behavioral and physiological stress responses, Injaian et al. 2018c; Mills et al. 2020).

The determinants of this flexibility are complex and linked to the survival optimization system (SOS), which involves integrative systems (central nervous and endocrine systems), and cognitive appraisal and learning systems (Mobbs et al. 2015). The plasticity of this SOS is certainly species-specific and genetically determined, but there is also evidence that it can vary between populations or individuals (Vincze et al. 2016; Grunst et al. 2021), and be affected by previous life experience (McCarty 2016a, b) and notably by early life. Cognition, learning abilities, brain structure, and the ontogeny of most integrative systems (endocrine and nervous systems) are indeed affected by developmental conditions, developmental stress (Welberg and Seckl 2001; McGowan and Matthews 2018), and more specifically noise pollution. For example, the ontogeny of the HPA axis is affected by exposure to noise pollution with a lower sensitivity of this axis to stress (i.e., reduced secretion of corticosterone in response to stress) in several (Kleist et al. 2018), but not all circumstances (Crino et al. 2013; Angelier et al. 2016). There is very little data to test if early-life exposure to noise pollution represents a constraint or if it orientates the SOS toward a functioning that will help the organism to cope with noise pollution later in life (Mariette et al. 2021). Current data suggest that developmental exposure to noise is associated with impaired learning and cognitive abilities (Osbrink et al. 2021), suggesting that early-life exposure to noise pollution may indeed reduce the flexibility of the SOS later in life. However, developmental exposure to noise pollution also seems to reduce the sensitivity of the HPA axis to stress (Kleist et al. 2018), and this may allow the organism to better cope with a stressful noisy environment later in life (e.g., Tennessen et al. 2018). Additional field

and experimental studies are definitely needed to better assess whether adaptive developmental programming occurs in the context of noise pollution.

9.5 Perspectives and Future Research Needs

9.5.1 Cumulative and Interactive Effects of Pollutants on Stress-Coping Mechanisms

The impact of these pollutants on human health and wildlife is now being increasingly studied and the current literature allows scientists and decision makers to assess, at least partly, the risk that each single pollutant represents to humans and biodiversity. Similarly, an increasing number of studies are investigating the impact of the characteristics of a given pollutant on the functioning of vertebrate organismal systems (e.g., the intensity of pollution). However, in the real world these pollutants often covary, and vertebrates are constantly exposed to a combination of them (Karlsson et al. 2021). In this context, there is an important gap in our understanding of the interactive and cumulative effects of these different types of pollutants on living organisms (Vermeulen et al. 2020), especially when referring to stress-coping mechanisms.

Firstly, it is important to understand if the co-occurrence of chemical pollutants and physical pollutants during the developmental period alters stress-coping mechanisms in a complex manner (cumulative, synergic or antagonist effects). Although data is currently lacking in this regard, a few studies suggest that such interactive effects may occur during the development. For example, Cory-Slechta and collaborators have reported that developmental exposure to lead and to developmental stress could indeed have interactive effects on multiple stress-coping mechanisms in rodents (i.e., catecholamines, HPA axis, Cory-Slechta et al. 2004, 2008; Rossi-George et al. 2009) with potential consequences in terms of performance and pathologies later in life (Virgolini et al. 2006).

Secondly, it is also crucial to understand if exposure to a specific pollutant alters the ability of the organism to cope with an additional pollutant. There is indeed evidence that chemical pollutants may disrupt stress-coping mechanisms, and therefore alter the ability of the organism to cope with stress. When the stress-coping mechanisms are not fully solicited, the deleterious impact of such chemical pollutants on fitness might remain limited, even if significant (Fig. 9.4). However, other additional pollutants may alter environmental conditions and their perception by the organism (e.g., physical pollutants). To cope with these pollutants, stress-coping mechanisms are crucial, and their disruption by a chemical pollutant may lead to ineffective and maladaptive responses. In that scenario, the occurrence of a second pollutant may exacerbate the detrimental impact of the first pollutant on health and performance (Fig. 9.4). To the best of our knowledge, there is no data to assess the pertinence of this hypothesis. A few studies have examined the impact of the

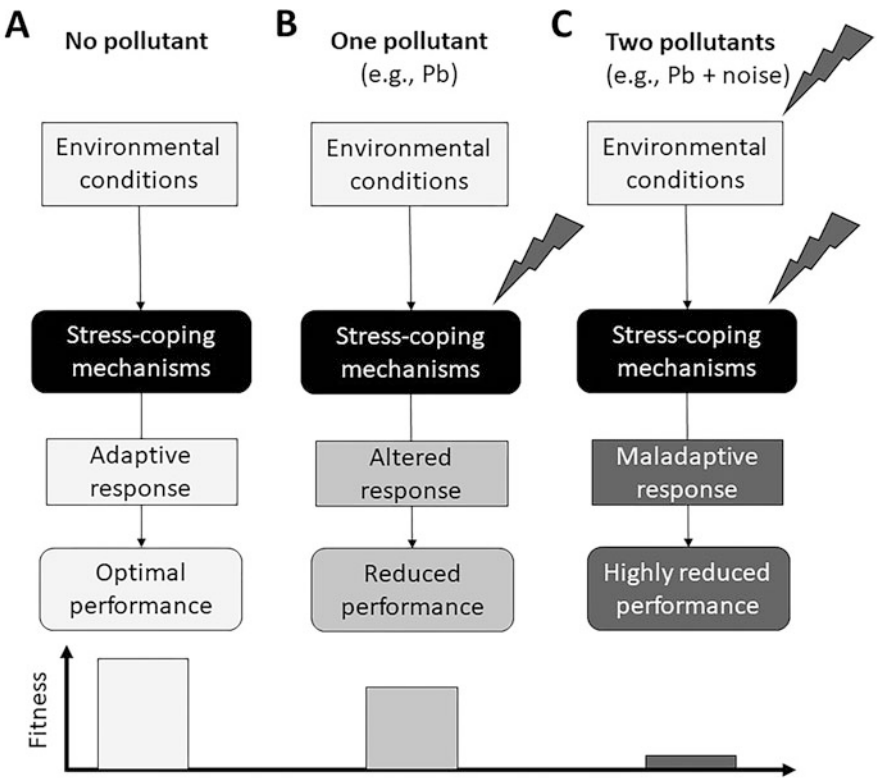

Fig. 9.4 Potential interactive effects of pollutants on stress-coping mechanisms and performance. In this diagram, three scenarios are described and they represent either an absence of pollutant (**a**), the occurrence of one pollutant (e.g., Pb) that disrupts stress-coping mechanisms (**b**), the occurrence of two pollutants (e.g., Pb and noise) that, respectively, disrupt stress-coping mechanisms and induce a stressful environmental situation (**c**). While stress-coping mechanisms are effective to optimize performance when pollutants are absent (**a**), a chemical pollutant (e.g., Pb) could disrupt stress-coping mechanisms (e.g., the HPA axis) and lead to a non-optimal stress response, and therefore to a reduced fitness (**b**). The co-occurrence of a chemical (Pb) and a physical (noise) pollutant could have dramatic effect on fitness, if lead alters the ability of the organismal stress response to cope with noise (**c**)

combination of two pollutants on human health or the performance of wild animals (e.g., Ferraro et al. 2020; Dominoni et al. 2020b), but none of these studies have focused on the importance of stress-coping mechanisms *per se*. For example, lead pollution and noise pollution occur simultaneously in the urban environment, but their potential interactive or cumulative effects on stress-coping mechanisms, human health, and wildlife have to the best of our knowledge never been investigated. We have previously described the importance of cognition and learning in determining the ability of individuals to adjust to noise pollution through habituation and through a better assessment of the costs that noise pollution may entail. However, we have also described the cognitive impairment that results from lead contamination during

the developmental period. Therefore, taken together, these results suggest that exposure to lead may alter the ability of urban individuals to cope with noise pollution through its impact on cognitive processes. Similarly, there is good evidence that exposure to lead can alter the integrative systems that govern the response to stress (fight or flight response and HPA axis), and more particularly it can result in an increased activation of these mechanisms in response to stress. However, a reduced sensitivity to stress may be required to cope with noise pollution to avoid the fitness costs of an overstimulation of stress-coping mechanisms in a context of stressful exposure to noise. Therefore, the impact of lead on these mechanisms may reduce the ability of individuals to adjust to noise pollution. Overall, this suggests that lead pollution could theoretically exacerbate the detrimental impact of noise pollution on health and performance.

Future experimental studies should now explicitly test this hypothesis of cumulative and interactive effects of pollutants on stress-coping mechanisms and fitness. They should specifically examine how the combination of multiple and various pollutants (physical and chemical pollutants) may interact and affect stress-coping mechanisms, individual performance, and health in humans and wild vertebrates.

9.5.2 Hormesis: An Overlooked Mechanism in Wild Vertebrates

This chapter has emphasized the importance of the developmental period to understand not only the impact of pollutants on performance, but also the ability of the organism to adjust to pollutants later in life. Most studies have reported that exposure to chemical pollutants is associated with health issues and reduced fitness, mainly because of the toxicological effects of the pollutants on organismal systems. As a result, the general agreement is that exposure to chemical pollutants will lead to pathologies, to disrupted stress-coping mechanisms, and to a lower ability to cope with pollutants later in life. However, exposure to chemical pollutants may counterintuitively improve the response of the organism to pollutants or stressors later in life by modifying the functioning of organismal systems (see Calabrese 2005 in the context of toxicology; see also Chap. 2). A few studies have shown that such dose-dependent responses to inorganic contaminants can occur in vertebrates. For example, Heinz et al. (2010) showed that prenatal exposure to low doses of methylmercury was associated with benefits in terms of hatching success in a bird species. Similarly, exposure to low levels of lead was associated with increased red blood cells production, while this effect was reversed at high concentrations (i.e., reduced RBC production, Iavicoli et al. 2003). Recently, it has been shown that exposure to a low dose of a mixture of chemical pollutants improved performance in terms of neurobehavioral tests in the rat (Tsatsakis et al. 2019).

In that context, specific attention should be given to the hormesis concept because it is thought to enhance phenotypic plasticity (Costantini et al. 2010), especially during the ontogeny of organismal systems. Indeed, priming hormesis suggests that developmental exposure to a mild stressor could improve the ability of the organism to cope with subsequent exposure to higher levels of that stressor (Costantini 2014a). Because central stress-coping mechanisms govern the response to multiple stressors, priming hormesis may even improve the ability of the individual to cope with other types of stressors. Although there is some evidence that exposure to mild challenging conditions early in life may be associated with better fitness (reviewed in Costantini et al. 2010), little data is available to test whether this effect is mediated by ontogenetic modifications of the functioning of stress-coping mechanisms in vertebrates. Priming hormesis has been extensively studied in the context of immunity and resistance to oxidative stress (Costantini 2014b), but much less in the context of the ontogeny of stress-coping mechanisms (i.e., the HPA axis, the fight or flight stress response). However, glucocorticoids are, for example, potential mediators of priming hormetic effects (Li et al. 2019) because (1) environmental conditions are known to influence the exposure of the developing organism to glucocorticoids and (2) developmental exposure to glucocorticoids often leads to dose-dependent effects on stress-coping mechanisms (Schoech et al. 2011; Crino and Breuner 2015; Eyck et al. 2019). For example, chronic exposure to glucocorticoids has been linked with cognitive impairment, while cognition may be in contrast improved in response to a temporary surge of circulating levels of glucocorticoids (de Kloet et al. 1999; Lupien et al. 2005). Future studies now need to examine whether contaminants induce dose-dependent effects on stress-coping mechanisms in vertebrates, and whether these effects are adaptive.

9.5.3 Microevolution

Finally, the ability of vertebrate populations to cope with a polluted world is not only determined by phenotypic plasticity, but also by evolutionary processes (Swaddle et al. 2015). Selection can drive the fate of vertebrate populations exposed to pollutants by favoring specific stress-coping strategies that are beneficial in response to pollutants. Support for such selective process comes from invertebrates with short generation times, such as mosquitoes that have become resistant to insecticides (Hemingway et al. 2002). In vertebrates, longer generation times may constrain the ability of most vertebrate species to adapt to pollutants, especially when these pollutants cannot be apparated to naturally occurring stressors or chemicals (Hawkins et al. 2019).

In some circumstances, microevolution may lead to resistance to pollutants in vertebrates. For example, resistance to pesticides has recently evolved in sea lampreys, an invasive fish (Christie et al. 2019). Recently, it has also been suggested that artificial light at night and noise pollution may represent a strong evolutionary driver to adapt to urbanization (Swaddle et al. 2015; Miranda 2017; Hopkins et al. 2018).

The importance of stress-coping mechanisms has rarely been highlighted in this context of adaptation to pollutants. However, and importantly, stress-coping mechanisms often show large inter-specific and inter-individual variabilities (e.g., Cockrem 2007; Moller 2010; Tablado et al. 2021), and as a result, they are also the target of microevolution processes (Guindre-Parker 2018). Indeed, comparative studies have shown that urbanization may select specific coping styles in vertebrates (Sadoul et al. 2021; Tablado et al. 2021; but see Iglesias-Carrasco et al. 2020). As explained earlier in this chapter, stress-coping mechanisms can be the target of pollutants. They also mediate the response of the organism to pollution, especially when pollutants can be apparated to stressors (Sect. 9.2). Therefore, stress-coping mechanisms may be key determinants of selective processes and may determine the ability of species to evolve resistance and adaptation to pollutants. Importantly, microevolution can probably select specific phenotypes in terms of stress-coping mechanisms but it can probably also act on developmental plasticity. In other words, selection may favor individuals that are able to mitigate the detrimental impact of pollutants on their development, either by resisting or by avoiding the pollutant, or by selecting developmental strategies that allow individuals to cope better with the pollutants later in life.

To the best of our knowledge, no study has, however, examined whether adaptation to pollutants is mediated by selective processes acting on these stress-coping mechanisms. Therefore, we believe that studying how stress-coping mechanisms evolve in response to pollutants (chemical and physical) represents a promising avenue of research to understand how some species (and not others) may adapt to our polluted world.

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