



INVITED REVIEW

Remodeling Ancestral Phenotypic Plasticity in Local Adaptation: A New Framework to Explore the Role of Genetic Compensation in the Evolution of Homeostasis

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Synopsis Phenotypic plasticity is not universally adaptive. In certain cases, plasticity can result in phenotypic shifts that reduce fitness relative to the un-induced state. A common cause of such maladaptive plasticity is the co-option of ancestral developmental and physiological response systems to meet novel challenges. Because these systems evolved to meet specific challenges in an ancestral environment (e.g., localized and transient hypoxia), their co-option to meet a similar, but novel, stressor (e.g., reductions in ambient pO₂ at high elevation) can lead to misdirected responses that reduce fitness. In such cases, natural selection should act to remodel phenotypic plasticity to suppress the expression of these maladaptive responses. Because these maladaptive responses reduce the fitness of colonizers in new environments, this remodeling of ancestral plasticity may be among the earliest steps in adaptive walks toward new local optima. Genetic compensation has been proposed as a general form of adaptive evolution that leads to the suppression of maladaptive plasticity to restore the ancestral trait value in the face of novel stimuli. Given their central role in the regulation of basic physiological functions, we argue that genetic compensation may often be achieved by modifications of homeostatic regulatory systems. We further suggest that genetic compensation to modify homeostatic systems can be achieved by two alternative strategies that differ in their mechanistic underpinnings; to our knowledge, these strategies have not been formally recognized by previous workers. We then consider how the mechanistic details of these alternative strategies may constrain their evolution. These considerations lead us to argue that genetic compensation is most likely to evolve by compensatory physiological changes that safeguard internal homeostatic conditions to prevent the expression of maladaptive portions of conserved reaction norms, rather than direct evolution of plasticity itself. Finally, we outline a simple experimental framework to test this hypothesis. Our goal is to stimulate research aimed at providing a deeper mechanistic understanding of whether and how phenotypic plasticity can be remodeled following environmental shifts that render ancestral responses maladaptive, an issue with increasing importance in our current era of rapid environmental change.

Introduction

Over the past several decades, our understanding of the role of phenotypic plasticity in adaptive evolution has gained considerable theoretical and empirical grounding (Schlichting and Pigliucci 1998; West-Eberhard 2003; 2005; Price et al. 2003; Schlichting 2004; Aubret et al. 2004; Yeh and Price 2004; Wund et al. 2008; Pfennig et al. 2010; Scoville and Pfrender 2010; Moczek et al. 2011; Mäkinen et al. 2015; Schneider and Meyer 2017). This growing body of work has demonstrated that the nature and magnitude of phenotypic plasticity can have a profound influence on the early stages of adaptive evolution

to novel environments. In particular, when phenotypic plasticity produces adaptive trait values in a novel environment, individuals may experience an increase in the probability of persistence (i.e., the Baldwin effect; Baldwin 1902; Pigliucci et al. 2006; Schlichting 2008; Chevin et al. 2010). Because population persistence is the first step toward reaching local fitness optima, this type of adaptive ancestral plasticity is widely regarded as playing a beneficial role in the early stages of local adaptation (reviewed in Levis and Pfennig 2016). Subsequent fine-tuning of adaptive plasticity toward a new local optimum may lead to adaptation by a process known as

genetic accommodation. Originally coined by West-Eberhard (2003), genetic accommodation is defined as “gene-frequency (evolutionary) change due to selection on variation in the regulation, form, or side effects of the novel trait in the subpopulation of individuals that express that trait” (Box 1 and Fig. 1). In other words, genetic accommodation is an adaptive process of selection on variation in reaction norms that moves a phenotypic expression to a new local fitness optimum.

Phenotypic plasticity, however, is not universally adaptive. Ancestral plastic responses can also have no effect on, or even reduce, organismal fitness in novel environments. Indeed, non-adaptive plasticity (Box 1) may be common in nature (Ghalambor et al. 2007; Storz et al. 2010b). Although the precise role of non-adaptive plasticity in evolution is not completely understood, several recent studies have demonstrated that it may be an important determinant of adaptive trajectories following the colonization of novel environments by initially increasing the strength of natural selection acting on colonizers and ultimately reshaping reaction norms (Ghalambor et al. 2007, 2015; Morris and Rogers 2013; Schaum and Collins 2014; Dayan et al. 2015; Fisher et al. 2016; Coulson et al. 2017; Ho and Zhang 2018). Here, we will deal with a specific type of non-adaptive plasticity that negatively affects fitness via the disruption of homeostasis (hereafter referred to as maladaptive plasticity; Box 1 and Fig. 1). We chose to focus on maladaptive plasticity because adaptation to suppress it requires the remodeling of ancestral developmental and physiological response systems. To clarify the role of maladaptive plasticity in adaptive evolution, we first review its causes and evolutionary consequences. We then outline a novel empirical framework for understanding the physiological and genetic mechanisms that allow for suppression of maladaptive plasticity. Our goal is to inspire research aimed at providing a deeper mechanistic understanding of how phenotypic plasticity can be remodeled during the course of adaptive evolution in novel environments.

The causes and consequences of maladaptive plasticity

The concept of maladaptive plasticity is perhaps best understood within the context of two environments: an ancestral environment in which a group of organisms has evolved, and a novel environment to which individuals from the ancestral population must adapt. The evolutionary consequences of maladaptive plasticity are manifest in situations where organisms

Box 1 Glossary of key terms

Adaptive plasticity: Any environmentally induced trait value that has a positive effect on fitness.

Genetic accommodation: Gene-frequency changes caused by selection in response to environmentally (or genetically) induced changes in the phenotype (West-Eberhard 2003). Genetic accommodation is a general processes by which selection acts on genetic variation in phenotypic plasticity to bring individuals toward the local adaptive optimum.

Genetic assimilation: a form of genetic accommodation in which environmentally induced phenotypes gradually become canalized and develop in the absence of the triggering environmental stimulus (Grether 2005).

Genetic compensation: A form of genetic accommodation in which ancestral phenotypes are restored in the presence of a phenotype-altering environmental stimulus (Grether 2005).

Maladaptive plasticity: A subset of non-adaptive plasticity in which an environmentally induced trait has a negative fitness consequence.

Non-adaptive plasticity: A general term referring to any phenotypic plasticity that has no effect or a negative on fitness.

Phenotypic plasticity: The phenomenon by which a single genotype is able to produce multiple phenotypes in response to an environmental stimulus.

Reaction norm: The range of phenotypes produced by a single genotype across a range of environments.

Set point: A target value of a regulated physiological variable (e.g., plasma osmotic pressure). Deviations from the set point, triggered by changes in the environment, result in plastic responses that, in some organisms, act to return the internal state to the set point value.

Threshold: Value of an internal environmental variable that, when crossed, triggers a plastic response to the environment.

find themselves outside of the range of environments to which they have evolved (e.g., by colonization or *in situ* environmental change), and result from a mismatch between the evolved response in the ancestral environment, and the optimal response in the novel one (Ghalambor et al. 2007; Crispo 2008; Sih et al. 2011). Maladaptive plasticity often stems from organismal responses that lead to the expression of phenotypes that, while adaptive or neutral in the ancestral context, reduce fitness when expressed in the new environment (i.e., the adaptive value of plastic responses is context dependent). The context dependency of the adaptive value of plasticity often results from the co-option of ancestral homeostatic response systems to solve novel, or ancestrally rare,

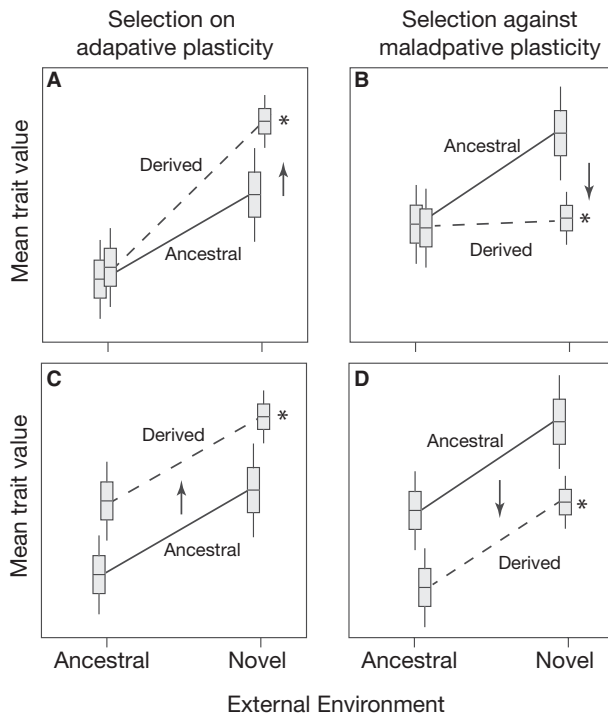


Fig. 1 Hypothetical reaction norms depicting selection on adaptive or against maladaptive plasticity and evolution by genetic accommodation. Figures depict hypothetical reaction norms under the ancestral and novel external environmental conditions. Solid lines represent an ancestral reaction norm, while dashed lines represent reactions norms of a hypothetical derived population that adapts to the novel environment. **A:** Selection on adaptive ancestral plasticity pulls the mean trait value that is expressed in the novel environment toward a new optimum (asterisk) by the process of genetic accommodation (West-Eberhard 2003). **B:** The ancestral reaction norm is maladaptive, and genetic compensation (a form of genetic accommodation; Grether 2005) results in a suppression of plasticity that reverts the derived trait value back toward the ancestral value. In this case, the optimal value in the novel environment approximates the ancestral value in the ancestral environment (represented by an asterisk), though this need not always be the case (Grether 2014). Both cases can hypothetically be achieved via selection on the slope of the reaction norm (A, B) or the intercept (C, D). Note that in all cases, derived trait variance is reduced compared with ancestral trait variance in the novel environment.

challenges; such co-option can lead to misdirected responses when these systems are induced in an attempt to solve a challenge that they did not evolve to surmount (Storz et al. 2010b). The expression of maladaptive plasticity in a novel environment can therefore expose cryptic genetic variation in reaction norms that is otherwise shielded from selection in the ancestral environment (Schlichting 2008). Once exposed, genetic variation in reaction norms can be selected upon.

The causes of maladaptive plasticity have been explored in a variety of contexts. Stress responses or

resource limitation in novel environments are often invoked as causes of maladaptive plastic responses (e.g., Ghalambor et al. 2007; Censer 2017). In these cases, maladaptive phenotypes are the product of a disruption of homeostasis or a deficiency in a key resource, which prevents the expression of optimal phenotypes. This homeostatic disruption or resource limitation restricts the portions of the reaction norm that are accessible in the novel environment. A now classic example outlined by Grether (2005) is that of Sockeye salmon (*Oncorhynchus nerka*). Ancestrally anadromous Sockeye mature in the Pacific Ocean and then return to freshwater lakes and rivers to breed. As Sockeye mature in the ocean, they transition from olive green to a brilliant red breeding coloration from pigments that are derived from dietary carotenoids (Craig and Foote 2001). Residuals, the progeny of Sockeye that fail to migrate back to the ocean, fail to develop red breeding coloration in these oligotrophic freshwater environments due to limitation in the availability of carotenoids. In this case, a lack of a key resource prevents the induction of a plastic phenotype; residuals remain olive green throughout maturity. Locally adapted landlocked forms of Sockeye (Kokanee), however, have evolved to surmount this maladaptive resource limitation by producing red breeding coloration via increases in carotenoid assimilation efficiency (Craig and Foote 2001), adaptively remodeling ancestral plasticity to restore the ancestral phenotype (Grether 2005). In cases like this, maladaptation arises because portions of an adaptive ancestral reaction norm cannot be accessed for phenotypic expression in a novel environment. Although a lack of phenotypic induction due to resource limitation is clearly maladaptive, we argue that viewing this phenomenon as maladaptive plasticity *per se* is not appropriate because a lack of phenotypic induction is difficult to envision as a plastic response.

In our view, a more appropriate definition of maladaptive plasticity is that which arises through expression of plastic responses that, while adaptive or neutral in an ancestral context, produce misdirected responses that reduce fitness in a novel environment (e.g., Storz et al. 2010b). In this case, phenotypic expression is not restricted by resource limitation; the entire reaction norm is accessible, but the induced response produces phenotypes that reduce fitness compared with the non-induced trait value. A prominent example of this phenomenon is the excessive red blood cell production (erythropoiesis) of lowland animals that are exposed to hypobaric hypoxia at high elevation (Storz et al. 2010b). The underlying cause of this misdirected response is

hypothesized to stem from an evolved response to anemia in lowland ancestors (Hebbel et al. 1978; Storz et al. 2010b). Both hypobaric hypoxia and anemia reduce levels of tissue oxygenation, but this effect is due to different underlying causes. Reduced tissue oxygenation due to anemia is caused by a reduction in blood oxygen carrying capacity due to insufficient hemoglobin concentration. Thus, the solution to anemia-driven tissue hypoxia is to increase hemoglobin via red blood cell production. In the case of hypobaric hypoxia, by contrast, reduced tissue oxygenation has an external cause—the reduced pO_2 of inspired air. Increasing red blood cell concentration under these circumstances may further compromise tissue oxygenation because of an associated increase in blood viscosity, which can limit cardiac output and convective oxygen transport (Villafuerte et al. 2004). In this case, co-option of ancestral homeostatic responses to anemia exacerbates the environmental challenges of high elevation environments. Many species that are native to high elevation have evolved compensatory physiological adaptations to prevent the induction of these maladaptive erythropoietic responses, maintaining hematocrit levels at high elevation that are typically within the range expressed by their lowland relatives that are living at low elevation (reviewed in Storz et al. 2010b). Similarly, *Ostreococcus* algae respond to high pCO_2 environments with accelerated growth rates, which reduce lifetime fitness by increasing rates of oxidative damage. Experimental evolution under high pCO_2 conditions results in a reversion back to ancestral growth rates (Schaum and Collins 2014). The difference between maladaptive plasticity that results from resource limitation versus a misdirected ancestral response is a subtle, but often overlooked, distinction.

Theory suggests that the expression of maladaptive plasticity in novel environments can facilitate adaptive evolution by increasing the strength of natural selection (Ghalambor et al. 2007, 2015; Fisher et al. 2016; Huang and Agrawal 2016; Coulson et al. 2017). This is because maladaptive phenotypes reduce fitness and thereby establish or intensify a selection gradient. For adaptation to proceed, therefore, natural selection must act on genetic variation that shifts the reaction norm in the direction of the new local optimum (Fig. 1; Price et al. 2003; Ghalambor et al. 2007, 2015; Conover et al. 2009; Storz et al. 2010b; Morris and Rogers 2013). Selection against reaction norms that reduce fitness is likely to be intense because these maladaptive reaction norms move trait values further from local adaptive optima compared with the non-induced state (Ghalambor et al. 2015; Fisher et al. 2016; Huang and Agrawal 2016).

Natural selection that acts to suppress maladaptive plasticity, or restore plasticity that is lost as a result of resource limitation, requires compensatory genetic change, a phenomenon termed “genetic compensation” by Grether (2005; Box 1). As originally defined by Grether (2005), genetic compensation is “a form of genetic accommodation (Box 1) in which the ancestral phenotypes are restored in the presence of a phenotype-altering environmental stimulus.” The original formulation of genetic compensation assumes that the phenotypic optimum in the novel environment would be equivalent to the optimum in the ancestral environment (Grether 2005). This need not be true in all cases. More recently, the concept of genetic compensation has been expanded to include selection that suppresses maladaptive plasticity to achieve an entirely new local optimum as well (Grether 2014; Morris and Rogers 2014). Although the evolutionary consequences of genetic compensation have been discussed extensively (Conover and Schultz 1995; Grether 2005; Ghalambor et al. 2007; Morris and Rogers 2013), we still lack an understanding of its physiological and regulatory underpinnings (Fisher et al. 2016). In particular, we lack a mechanistic understanding of how genetic compensation may act on homeostatic regulatory mechanisms to allow for the maintenance of ancestral phenotypes in the face of “a phenotype-altering environmental stimulus.”

We argue that a mechanistic perspective will provide key insights into the realized outcomes of genetic compensation, and the general importance of maladaptive plasticity in local adaptation. Further, a deeper mechanistic understanding of how phenotypic plasticity is remodeled following environmental shifts may be useful in predicting which species might be most vulnerable to rapid environmental change. In what follows, we outline a novel empirical framework to gain these mechanistic insights. We first consider how to identify maladaptive plasticity and genetic compensation in natural populations, and then we outline a novel framework to gain mechanistic insight into the role that genetic compensation plays in local adaptation of homeostatic regulatory systems. We argue that genetic compensation can lead to the evolution of homeostatic regulatory mechanisms that suppress maladaptive plasticity through two alternative strategies; to our knowledge these strategies have not been formally recognized by previous workers. We close by proposing new hypotheses for the conditions under which these alternative strategies are likely to evolve, and provide suggestions for an empirical framework to test them.

Detecting maladaptive plasticity and evolution by genetic compensation

Identifying genetic compensation requires a common-garden or reciprocal-transplant approach; to detect local adaptation of plasticity of any kind, one must compare reaction norms in at least two distinct taxa (e.g., Wund et al. 2008). In such experiments, individuals from ancestral and derived populations are raised in—or experimentally subjected to—the conditions that differ between ancestral and novel environments (e.g., Conover and Schultz 1995). The experiment is ideally conducted on laboratory-bred isogenic lines to isolate genotypic and environmental influences on phenotypic expression, but they can also be performed on outbred individuals that are born and reared in the lab to reduce the influence of environmental and/or maternal epigenetic effects.

Genetic compensation can be identified by comparing reaction norms (i.e., phenotypic values in response to two or more environments) between an ancestral and a derived taxon (Fig. 1). The defining signatures of genetic compensation are as follows: (1) the phenotypic value induced by the novel environment shifts toward the ancestral value in the ancestral environment (Fig. 1B). When genetic compensation acts to suppress maladaptive plasticity (as when ancestral responses are inappropriately co-opted in novel contexts; see above), this will result in a reduced reaction norm slope (Fig. 1B), or a downward shift of the intercept with no change in slope (Fig. 1D). This is true regardless of whether the ancestral reaction norm is positive (as shown in Fig. 1) or negative in slope. (2) Evolutionary change in plasticity must be adaptive in the novel environment. Therefore, if the novel environment induces a maladaptive increase in the trait value in the ancestor, an evolutionary pattern that is consistent with genetic compensation would be one in which the derived taxon evolves to express a reduced trait value in the novel environment (Fig. 1B). The resulting phenotypic value in the derived taxon in the novel environment may be closer, or equivalent to, the ancestral value that is expressed in the ancestral environment (Grether 2005). Note that the processes of genetic compensation is in contrast to that typically envisioned for genetic assimilation in which selection acts on phenotypic plasticity to canalize the expression of an adaptive phenotypic value that was originally environmentally induced in a novel context (West-Eberhard 2003).

One assumption that is implicit in this approach is that ancestral plasticity reduces fitness in the novel environment. Due to a variety of logistical

constraints, most studies that have identified this pattern of genetic compensation have not directly measured the fitness consequences of ancestral plasticity. Instead, these fitness consequences are inferred from the values of fitness-related traits (e.g., growth rate; Handelsman et al. 2013). While direct assessment of the fitness effects of induced trait values in alternative environments remains the gold standard, there are a number of non-mutually exclusive approaches that can feasibly be used to indirectly infer fitness effects. Although a discussion of these approaches is beyond the scope of this review, linking a derived trait value to fitness gains in the novel environment is nonetheless a requirement for identifying genetic compensation.

Genetic compensation and the evolution of homeostatic regulatory systems

As outlined above, genetic compensation can be viewed as an evolutionary process by which selection on genetic variation in developmental, physiological, and regulatory phenotypes acts to suppress maladaptive plasticity in a novel environment. In the classic formulation of genetic compensation, selection acts to restore the ancestral phenotypic value in the presence of a novel environmental stimulus because the induced change is maladaptive. Given their central role in the regulation of basic physiological function, we argue that the maintenance of the ancestral phenotype in the face of a novel stimulus will often be achieved by modifications of homeostatic regulatory systems, and these systems therefore are likely to be common targets of genetic compensation. Further, we argue that genetic compensation to suppress maladaptive plasticity via the modification of homeostatic systems occurs through two general strategies. These alternative strategies can be broadly categorized as tolerance or resistance, and they are distinguished by whether internal physiological variables (e.g., arterial O₂ saturation, plasma ion concentration) that serve as cues for induction of plastic responses are altered from the ancestral state (Fig. 2).

Under a tolerance strategy, changes in the intensity or type of external environmental stressor (e.g., O₂ partial pressure, salinity) in a novel environment induces a maladaptive plastic response in the ancestor, which is suppressed in the derived population by altering the value of the internal cue that initiates the plastic response (Fig. 2B). The effect of altering this threshold is that changes in the internal environment are “tolerated” without stimulating a plastic response (Fig. 2B). The tolerance strategy, therefore, prevents the expression of maladaptive phenotypes over the

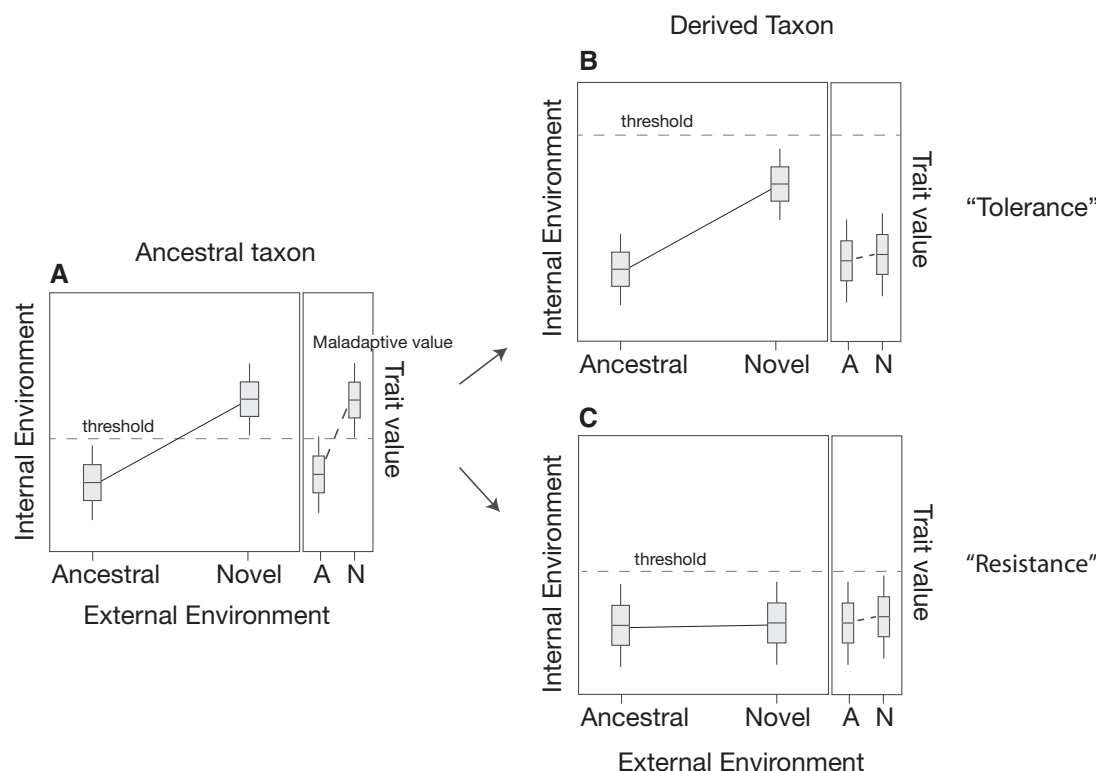


Fig. 2 Tolerance and resistance strategies are two mechanisms by which maladaptive plasticity is suppressed by genetic compensation. Figures show the values for the internal environment (leftmost panels) and induced trait (rightmost panels) in relation to ancestral (A) and novel (N) external environmental conditions. Panel **A** shows the ancestral pattern: the novel external stimulus yields an internal environment value that induces maladaptive plasticity. This induction is triggered when the internal environmental value crosses a threshold. Panels **B** and **C** represent the outcomes of genetic compensation in a derived taxon that adapts to the novel environment over an unspecified time period. In both cases, genetic compensation reduces plasticity such that traits in the novel environment approach the ancestral values. Tolerance (**B**) occurs when the internal response to the novel environment is maintained but the threshold shifts. Resistance occurs when the internal environment is buffered against the novel external stimulus (and the threshold may remain unchanged). In both cases, the maladaptive trait value is no longer induced because the internal value does not cross the threshold.

ecologically relevant range of external conditions that exist in the novel environment, despite alteration of the internal state of the organism.

Grether (2014) describes a potential example of genetic compensation that would qualify as a tolerance strategy under our framework. Exposure to endocrine disrupting chemicals (EDCs) is associated with a variety of developmental and physiological abnormalities in many animals because they mimic or block the action of endogenous hormones (Scholz and Mayer 2008). As noted by Grether (2014), “any evolutionary response that reverses the phenotypic effects of endocrine disruption would qualify as genetic compensation,” and if this compensation occurs without alteration of endogenous hormone or EDC titers, it would qualify as a tolerance strategy. Dioxins are powerful EDCs that bioaccumulate in aquatic food chains (Giesy et al. 1994). Dioxin exposure results in homeostatic disruption of several development processes and physiological pathways,

which ultimately results in a range of adverse outcomes, including physical deformities and embryonic lethality (Giesy et al. 1994; Karchner et al. 2006). Many of these adverse effects are caused by altered gene expression that is induced by dioxin via activation of the ligand-dependent transcription factor, aryl hydrocarbon receptor (AHR) (Burbach et al. 1992); dioxin serves as an internal cue for the induction of gene expression changes that result in maladaptive phenotypic responses. However, several aquatic, piscivorous bird species, including the Common Tern (*Sterna hirundo*), are regularly exposed to high levels of dioxins in the environment. Correspondingly, Common Terns have evolved a nearly 250-fold reduction in the sensitivity to dioxin compared with chickens (*Gallus gallus*). This reduced dioxin sensitivity is achieved by a reduction in AHR binding affinity for dioxin that results in a parallel reduction in transcriptional transactivation (Karchner et al. 2006), effectively increasing the set

point for the induction of maladaptive transcriptional responses to dioxin exposure.

An alternative mechanism of genetic compensation is what we have termed resistance (Fig. 2C). Under a resistance strategy, the ancestral internal threshold that induces plasticity remains unchanged in the derived lineage (Fig. 2C). Instead, genetic compensation proceeds through selection on genetic variation that allows individuals to maintain internal conditions within the bounds of the ancestral homeostatic set point despite changes in the external environment. The defense of these ancestral internal conditions can be achieved via compensatory changes that alter the capacity of steps in integrated physiological pathways that impinge on them.

Consider the oxygen transport cascade of air-breathing vertebrates as an example for the evolution of resistance strategies. Arterial O₂ saturation can be maintained despite the reduction in the partial pressure of oxygen at high elevation via changes in breath rate, the capacity for pulmonary O₂ diffusion, and/or blood oxygen carrying capacity (Storz et al. 2010a; Cheviron and Brumfield 2012), all of which safeguard arterial O₂ saturation, the set point that is monitored by glomus cells in the carotid body and other oxygen-sensing chemoreceptors (Prabhakar 2000). In addition to excessive erythropoiesis, several other plastic responses to transient and localized hypoxia that evolved in lowlanders are also maladaptive under the chronic hypoxic conditions at high elevation because they can limit O₂ delivery (e.g., global constriction of pulmonary and cerebral vasculature, or right ventricle hypertrophy) and contribute to pathophysiological conditions such as chronic mountain sickness and pulmonary edemas (Rivera-Ch et al. 2007; Storz et al. 2010b; Simonson 2015). Animals with a long evolutionary history in high elevations very often show a suppression or complete loss of the maladaptive responses that can limit O₂ delivery (Durmowicz et al. 1993; Groves et al. 1993; Ge et al. 1998; Sakai et al. 2003; Beall 2007; Beall et al. 2010; Storz et al. 2010b; Velotta et al. Forthcoming 2018), suggesting widespread genetic compensation. Deer mice (*Peromyscus maniculatus*) that are native to high elevations (4350 m asl), for example, are able to maintain 6–8% greater arterial O₂ saturation under hypoxia exposure, compared with mice from low elevations (430 m asl) (Tate et al. 2017), and this increased arterial O₂ saturation is associated with modifications in upstream portions of the O₂ transport cascade that increase pulmonary O₂ extraction and blood oxygen carrying capacity (Storz et al. 2009, 2010b; Natarajan et al. 2013; Lui et al. 2015; Ivy and Scott 2017; Tate et al.

2017; Dawson et al. 2018). Such compensatory changes can attenuate the expression of maladaptive plasticity because changes in the external environment are not detected at the level of the internal set point. Indeed, the safeguarding of arterial O₂ saturation is associated with blunted erythropoietic and vasoconstrictive responses in highland deer mice (Lui et al. 2015; Velotta et al. Forthcoming 2018), suggesting genetic compensation of maladaptive plasticity via resistance.

Recall that maladaptive reaction norms arise through at least two common causes, resource limitation and co-option of ancestral homeostatic systems that produce misdirected phenotypic responses. We argue that the tolerance or resistance strategies that are outlined above should often evolve in cases where maladaptation is the result of the inappropriate co-option of ancestral response systems, but not in cases where maladaptation results from resource limitation. The example of Sockeye salmon breeding coloration provides a good illustration of why this is the case. In Sockeye, the initial maladaptation resulted from a failure to induce a change in breeding coloration in resource-limited environment, whereas the derived adaptive state in Kokanee salmon restored the expression of breeding coloration via genetic compensation on carotenoid assimilation efficiency. Thus, selection acted on assimilation efficiency to restore ancestrally adaptive plasticity. Under tolerance and resistance strategies, selection necessarily acts against a maladaptive reaction norm that leads to inappropriate phenotypic expression in a novel context. In other words, resource limitation results in maladaptation because a trait cannot be expressed, whereas misdirected co-option of ancestral homeostatic response systems results in the expression of a maladaptive phenotype.

What conditions favor the evolution of tolerance and resistance strategies?

Tolerance and resistance are two alternative mechanisms of genetic compensation that are not mutually exclusive. Organisms may utilize both strategies to suppress maladaptive plasticity upon colonization of novel environments, but there may be general conditions where we might expect one or the other strategy to evolve. We argue that a strong predictor of these conditions may be the structure and genetic architecture of the specific physiological and regulatory systems that elicit plastic responses.

Physiological considerations

To understand how the structure of physiological systems may influence the likelihood that tolerance

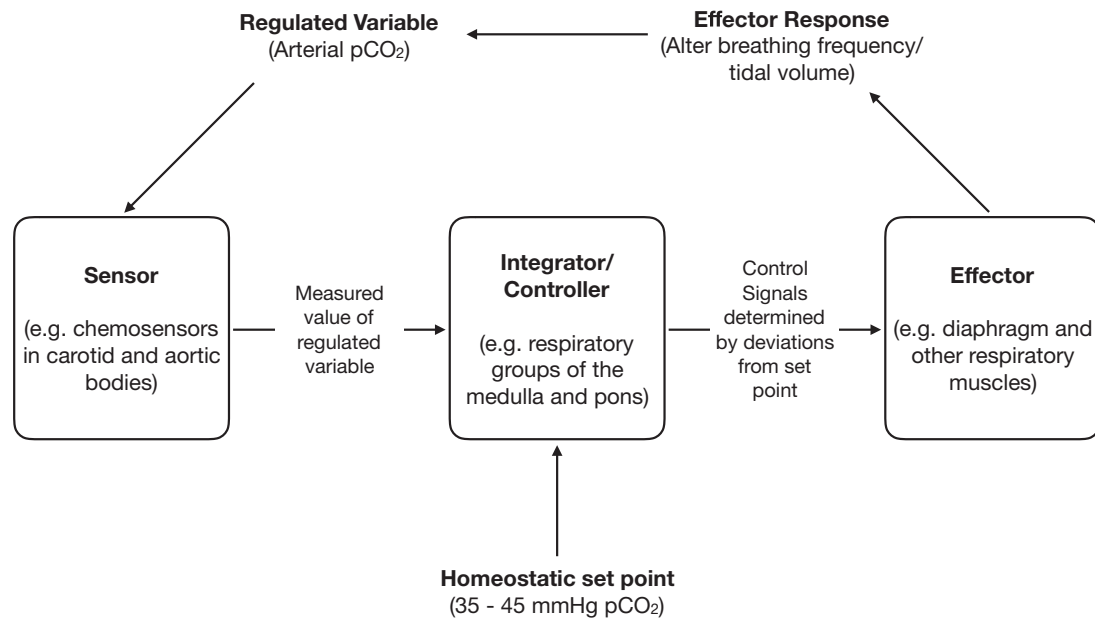


Fig. 3 Simple model of a homeostatic regulatory system. Examples of the generic model components are illustrated using the mammalian negative feedback system that regulates arterial $p\text{CO}_2$ within the bounds of a set point range (roughly 35–45 mmHg in humans). Changes in arterial $p\text{CO}_2$ are detected by peripheral and central chemoreceptors that act as sensors, transmitting signals to integrator and control systems in the respiratory center of the brainstem. Integrators and controllers in the brainstem detect deviations from the set point range and transmit signals to the diaphragm and other respiratory muscles to restore $p\text{CO}_2$ toward the set point. The diaphragm and respiratory muscles serve as effector systems, altering breath rate and/or tidal volume to effect change in the regulated variable, $p\text{CO}_2$, to return it to the bounds of the homeostatic set point. Figure modified from Modell et al. (2015).

and resistance strategies will evolve, consider a simple model of a homeostatic feedback loop (Modell et al. 2015; Fig. 3). This model consists of four components that form an integrated response system that stimulates plastic responses to maintain physiological conditions within a certain range. These components are (1) sensors, which measure values of internally regulated variables (e.g., pH, ion concentration, temperature); (2) integrators, that interpret signals from sensors and detect deviations from the normal range of a regulated variable (i.e., deviations from a set point); (3) controllers, that interpret signals from the integrators and determine the appropriate response to return the regulated variable to a set point; and (4) effectors, physiological elements that determine the value of a regulated variable. The specific functions of each of these components make them more or less likely to be the targets of either tolerance or resistance strategies.

Given their central role in cue sensing, genetic compensation via modification of sensors is likely to proceed through a tolerance strategy. Alteration of the internal cue that elicits a plastic response may proceed through modifications of the sensitivity or precision with which a sensor can measure the internal environment. A prime example of how a sensor may evolve to alter a homeostatic set point can

be found in hibernating 13-lined ground squirrels (*Ictidomys tridecemlineatus*). During hibernation, 13-lined ground squirrels tolerate severe reductions of body temperature (down to $\sim 5^\circ\text{C}$), which reduces their basal metabolic rates (BMRs) to just 5% of their non-hibernating BMR (Geiser 2004; Brown et al. 2012; Kisser and Goodwin 2012). The suppression of body temperature during hibernation in ground squirrels is associated with a reduction cold sensitivity in TRPM8, a non-selective cation channel that serves as a general somatosensory cold sensor in mammals (Matos-Cruz et al. 2017); loss of sensitivity to cold via TRPM8 functional modification results in the tolerance of a lower body temperature. Similarly, because they receive and process information that is provided by sensors, tolerance strategies may also evolve through mechanisms that blunt signal processing and transmission through integrator and controller systems. Again, this mechanism may alter the value of the internal cue that is needed to elicit a plastic response, but in this case, the modification is not to the system that senses the internal state, but rather the system that interprets these signals and leads to the stimulation of a response.

Conversely, resistance strategies are most likely to evolve through modification of effectors because these systems directly influence the value of the

regulated variable. Altering the capacity of effector systems provides the means to buffer internal environmental conditions in the face of changes to the external environment. Doing so provides a means of maintaining the regulated variable within the bounds of the ancestral set point, and thereby repressing the ancestral response that is maladaptive in the novel environment. As discussed above, alteration of steps in the oxygen transport cascade that safeguard arterial O_2 saturation in highland mammals provides an example. Here, increases in pulmonary O_2 extraction and blood O_2 carrying capacity safeguard arterial O_2 saturation in the face of hypobaric hypoxia. Increases in the capacity of these effector systems maintain arterial O_2 saturation within the bounds of the ancestral homeostatic set point, preventing the induction of maladaptive plastic responses that can hinder O_2 delivery. Thus, the specific functions of the physiological components that comprise homeostatic feedback loops may predispose them to being involved in the evolution of resistance or tolerance strategies of genetic compensation.

Similarly, predicting whether tolerance or resistance is more likely to evolve will depend on the degree of pleiotropic constraint associated with alteration of internal homeostatic set points. Because many physiological systems serve to maintain cellular environmental conditions within tightly regulated bounds, many interdependent systems have evolved to operate within these boundaries. For example, intracellular ion concentrations of vertebrates are tightly controlled around 300 mOsm/kg (Schmidt-Nielsen 1997), in turn, many proteins and cellular processes are under strong functional constraint to operate within these bounds (Zera 2011). Alteration of homeostatic set points for physiological systems that underlie intracellular ion balance would therefore require large-scale compensatory changes to maintain function of many individual proteins. Under these conditions, a tolerance strategy, which requires set point alteration, seems unlikely to evolve. Indeed, many homeostatic set points have deep evolutionary roots, and regulate fundamental physiological processes. It may be the case the pleiotropic constraints associated with set point alteration may render tolerance strategies difficult to achieve, at least on the timescales associated with population colonization of novel environments – the scale at which genetic compensation is typically invoked (but see the example of evolved reductions dioxin sensitivity in Common Terns discussed above). If so, selection should favor the resistance strategies that suppress maladaptive plasticity while safeguarding the ancestral homeostatic set point, because these strategies are less pleiotropically constrained.

Genetic considerations

The genetic architecture of ancestral plastic responses is also likely to influence the evolution of these alternative modes of genetic compensation. A variety of models for the genetic basis of phenotypic plasticity have been widely discussed (Via and Lande 1985; Scheiner and Lyman 1989, 1991; Gomulkiewicz and Kirkpatrick 1992; Schlichting and Pigliucci 1993, 1995; Via 1993; Via et al. 1995; Lande 2009). Under these models, plasticity is alternatively envisioned as either an emergent property that results from selection on different optimal trait values in alternative environments (e.g., Via and Lande 1985; Via 1993), or the direct result of the action on regulatory loci that govern environmentally-induced changes in structural gene expression (e.g., Schlichting and Pigliucci 1993, 1995). These alternative conceptualizations of plasticity have implications for genetic variation in reaction norms, and thus the potential genetic basis of genetic compensation. When plasticity is an emergent property of selection on optimal trait values in alternative environments, the evolution of phenotypic plasticity reduces to the familiar process that governs the evolution of any quantitative trait, and the genetic architecture of phenotypic plasticity is simply the architecture of trait values that are expressed under the alternative conditions. When plasticity is the direct result of the action of regulatory loci, phenotypic plasticity may have a genetic basis that is independent of that which underlies variation in the expressed trait value (Schlichting and Pigliucci 1993, 1995; Schlichting and Smith 2002). Under this conceptualization, genetic variation in reaction norms may result from allelic variation at both regulatory loci that underlie the induction of the plastic response as well as loci that influence the induced trait value.

Our intention is not to critically assess these models; both have theoretical and empirical grounding, and are likely to be supported in different contexts (Via et al. 1995). Instead, our intention is only to point out that these models have implications for the likelihood that tolerance or resistance strategies will evolve. Recall that the genetic architecture of plasticity that evolves as an emergent property simplifies to that of the phenotypic expression of trait values in those environments. For genetic compensation, the architecture of interest is that which underlies the expression of the maladaptive portion of the reaction norm. When these architectures are complex, composed of many loci of relatively small effect, direct evolution of the reaction norm may be unlikely

(Eyre-Walker 2010; Rajon and Plotkin 2013). Instead, resistance strategies that prevent the expression of conserved reaction norms may be a more effective form of genetic compensation, assuming that the architectures of these traits are not subject to similar constraints. When plasticity evolves via mutations that directly induce plasticity (e.g., transcription factors, *cis*-regulatory elements, etc.), direct evolution of the reaction norm may be more likely, and this potentially simpler genetic architecture may be more permissive for the evolution of tolerance strategies.

A simple approach for testing between tolerance and resistance strategies

Given the physiological and genetic considerations outlined above, it seems that genetic compensation that acts on homeostatic systems may proceed via the evolution of resistance strategies under most conditions. Empirically testing this hypothesis requires a new experimental framework for identifying alternative strategies of genetic compensation. In this section, we outline suggestions for a simple framework that could be used to determine whether homeostatic systems have evolved via tolerance or resistance strategies. A comparative approach to the application of this framework could provide empirical data to begin to generalize the conditions under which these alternative strategies evolve.

Discerning between tolerance and resistance strategies of genetic compensation requires the measurement of both the external environment (as in Fig. 1) and the internal environmental variable that serves as a set point for the induction of plasticity (Fig. 2). With respect to well-known homeostatic systems, relevant examples include: ambient O₂ partial pressure vs. arterial O₂ saturation or ambient osmotic pressure vs. plasma osmotic pressure. We assume that researchers have first experimentally detected evidence of genetic compensation in the trait(s) of interest in the colonizers of a novel environment (Fig. 1). In the ancestral taxon, the novel external environment causes a change in the internal environment that triggers a fitness-reducing response (Fig. 2A); this is of course a defining characteristic of maladaptive plasticity. In the derived taxon, the evolution of resistance or tolerance can be distinguished by whether the internal environment is buffered against changes in the external environment (resistance) or not (tolerance).

Under a tolerance strategy, the novel external environment will induce the same change in internal environment between ancestral and derived taxa

(Fig. 2B). However, this change in internal environment no longer leads to the expression of a maladaptive trait value in the derived, locally-adapted taxon in the novel environment. That is, the change in internal environment fails to trigger the ancestral maladaptive response. The pattern observed in Fig. 2B is caused by a shift in, or loss of, the threshold that triggered the plastic response in the ancestor. In this way, changes in the internal state are tolerated in that they do not lead to the induction of a maladaptive plasticity.

Figure 2C illustrates a pattern consistent with a resistance strategy. Here, the change in external environment does not result in a change in the internal environment in the derived taxon. This is because the derived taxon has evolved a compensatory mechanism(s) that safeguards the internal environment against external environmental variation. Because the internal environment is now buffered, the maladaptive trait value is not expressed (Fig. 2C). Note that because of this buffering, the threshold need not change under a resistance strategy. Thus, measuring the internal environmental variable that serves as the threshold for triggering plasticity within the context of the external environmental variation is both necessary and sufficient to discern between tolerance and resistance strategies. Application of this simple experimental framework can help to determine whether resistance is indeed the more common mode of genetic compensation in homeostatic systems as we suggest. Moreover, by identifying the general strategy of genetic compensation, this framework can serve as a springboard for more in depth studies of the mechanisms that underlie the remodeling of ancestral physiology in the process of local adaptation and how quickly such remodeling may evolve.

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