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SYMPOSIUM

Epigenetic Potential as a Mechanism of Phenotypic Plasticity in Vertebrate Range Expansions

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Synopsis During range expansions, organisms are often exposed to multiple pressures, including novel enemies (i.e., predators, competitors and/or parasites) and unfamiliar or limited resources. Additionally, small propagule sizes at range edges can result in genetic founder effects and bottlenecks, which can affect phenotypic diversity and thus selection. Despite these obstacles, individuals in expanding populations often thrive at the periphery of a range, and this success may be mediated by phenotypic plasticity. Increasing evidence suggests that epigenetic mechanisms may underlie such plasticity because they allow for more rapid phenotypic responses to novel environments than are possible via the accumulation of genetic variation. Here, we review how molecular epigenetic mechanisms could facilitate plasticity in range-expanding organisms, emphasizing the roles of DNA methylation and other epigenetic marks in the physiological regulatory networks that drive whole-organism performance. We focus on the hypothalamic-pituitary-adrenal (HPA) axis, arguing that epigenetically-mediated plasticity in the regulation of glucocorticoids in particular might strongly impact range expansions. We hypothesize that novel environments release and/or select for epigenetic potential in HPA variation and hence organismal performance and ultimately fitness.

Introduction

Environments are changing rapidly, in large part due to human activity, and it is becoming increasingly important to determine how organisms will respond (Ghalambor et al. 2007). One particularly important aspect of anthropogenic environmental change is the alteration of the geographical distributions of species. With increased urbanization and massive increases in global commerce, many individuals and populations are experiencing pressure to either change their native ranges or survive in novel areas (Parmesan and Yohe 2003). During such range expansions, organisms are often exposed to multiple pressures, including novel enemies (i.e., predators, competitors, and/or parasites) and unfamiliar or limited resources (Martin et al. 2015; Wingfield et al. 2015). Small propagule sizes at range-edges can also result in genetic founder effects and bottlenecks, which can affect phenotypic diversity and thus selection outcomes (Perez et al. 2006). Despite these obstacles, individuals in expanding populations often thrive at the periphery of a range, exhibiting extensive phenotypic differentiation from individuals near the range-core, a phenomenon called a genetic paradox (Perez et al. 2006). Given the low genetic diversity of most range-edge populations, high phenotypic variation at the range-edge is likely partially underlain by phenotypic plasticity (Richards et al. 2006; Ghalambor et al. 2007; Martin and Liebl 2014). Phenotypic plasticity, including both irreversible (i.e., developmental plasticity—West-Eberhard 2005) and reversible (i.e., phenotypic flexibility—Piersma and Drent 2003) forms, is likely to be common at range-edges because it allows for more rapid responses to novel environmental challenges than would be possible via genetic adaptation (Pigliucci 2001; Wright et al. 2010; Forsman

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2015). Moreover, several studies from the plant literature suggest that epigenetic mechanisms may underlie plastic responses to novel environments (Bossdorf et al. 2008; Angers et al. 2010; Bossdorf et al. 2010; Nicotra et al. 2010; Richards et al. 2012; Zhang et al. 2013a); however, similar studies in vertebrates remain scarce.

Here, we review how molecular epigenetic mechanisms could be driving plasticity in range expansions, emphasizing the roles of DNA methylation and other epigenetic marks in the physiological regulatory networks (PRNs) that drive whole-organism performance (Cohen et al. 2012; Martin and Cohen 2014; Martin et al. 2016b). As an example, we focus on the hypothalamic-pituitary-adrenal (HPA) axis, arguing that epigenetically-mediated plasticity in the regulation of glucocorticoids (GCs) might strongly impact the outcomes of range expansions. We hypothesize that novel environments release and/or select epigenetic potential; genotypes/species with a greater disposition to regulate performance adaptively via epigenetically mediated changes in GC regulation are apt to be those comprising most new populations. Below, we first provide evidence that GCs are involved in current and ongoing changes in the distributions of species. We then introduce then discuss the novel concept of epigenetic potential, and review evidence for how GCs might be regulated by (and even regulate) epigenetic potential. We close by offering a few promising options for future research.

GC regulation and range expansions

Maintenance of homeostasis is crucial for survival (Romero et al. 2009; Wingfield 2013), particularly at range-edges where individuals encounter novel challenges with which they have little to no evolutionary history (Liebl and Martin 2012). In vertebrates, endurance of and recovery from stressors (including novel ones) involve the coordinated regulation of GCs by the HPA axis (Romero et al. 2009; Wingfield 2013). Encounters with stressors typically result in a rapid increase in circulating GCs, which promote short-term survival via coordination of a broad range of physiological and behavioral responses (Addis et al. 2011). Stressor-induced GCs, in particular, play a pivotal role in integrating sub-organismal processes to match individual physiology and behavior to threats and opportunities in the environment (Martin et al. 2011; Lema and Kitano 2013; Martin et al. 2016a; Taff and Vitousek 2016).

Several studies also support GCs as physiological mediators of vertebrate range expansions, particularly birds. For example, in a study comparing GC responses among subspecies of white crowned sparrow (*Zonotrichia leucophrys*), populations at the range-edge (and a higher altitude) had significantly higher baseline and stress-induced levels of the avian GC, corticosterone (CORT), than populations near the range-core (i.e., lower altitude) (Addis et al. 2011). Moreover, several studies investigating the ongoing and recent range expansion of the introduced house sparrow (*Passer domesticus*) across Kenya (Liebl and Martin 2012; Martin and Liebl 2014) and Senegal (Martin et al. 2017) found that individuals at the range-edge secreted more CORT in response to an acute stressor (Liebl and Martin 2012; Martin and Liebl 2014). In Kenya, range-edge birds also expressed different levels of GC receptors (i.e., mineralocorticoid receptor—MR and GC receptor—GR) (Liebl and Martin 2013) in hippocampi compared with individuals residing near the site of introduction.

Whereas these studies are among the first to implicate GC regulation as important to range expansion success, the extent to which these patterns are underlain exclusively by plasticity remains unclear (Nussey et al. 2007; Martin and Liebl 2014). Selection for particular genotypes is also tenable, particularly because aspects of the HPA are heritable in vertebrates (Wust et al. 2004), which may help explain consistent differences among individuals in GC regulation. However, regulatory plasticity within the HPA-axis (or the capacity to alter GC regulation across time or context) is likely to be of particular importance at range-edges (Martin and Liebl 2014), especially for populations currently undergoing range expansion. The HPA axis is inherently plastic, as a critical mediator of organismal homeostasis. Further, plasticity can manifest much more rapidly than genetic variation, especially in the case of the oftentimes-small population sizes that occur at range-edges (Ghalambor et al. 2007). For example, evolutionarily unfamiliar stressors (e.g., novel foods, predators, or pathogens) may elicit a sub-optimal GC response (under- or over-exuberance) at range-edges, yet high HPA plasticity may allow individuals to fine-tune their responses to the environment contingent on risk and experience. Moreover, because GCs affect learning and memory (Sweatt 2009), plasticity in HPA regulation may underlie plasticity in behaviors important for fitness in novel environments (e.g., vigilance, exploration, aggression).

Epigenetically-mediated variation within the HPA

The regulation of GCs by the HPA axis is complex, involving multiple pathways, cells, and tissues at which variation can occur (Lema and Kitano 2013). Variation in any one element can affect the

capacity of individuals to coordinate crucial physiological and/or behavioral responses (Lema and Kitano 2013; Martin and Liebl 2014). There is increasing evidence that GC regulatory plasticity is partially mediated by environmentally-induced epigenetic variation. DNA methylation, histone modification, and other processes can affect nearly every component of the HPA axis (Fig. 1; Supplementary Table S1). The hypothalamus plays an especially crucial role in HPA activity; it transduces sensory information (e.g., the perception of a stressor arising from the amygdala or prefrontal cortex) into a physiological response (e.g., initiation of a stress response) (Smith and Vale 2006). Activation of the HPA axis involves the release of corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) from the hypothalamus, both of which are required for the stimulation/secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary and subsequent synthesis and release of GCs from the adrenal cortex (Smith and Vale 2006). As emphasized in Fig. 1, epigenetic variation resulting in differences in either CRF or AVP expression could have substantial consequences for the regulation of downstream physiological and/or behavioral responses to stressors. In rodents, several studies have found that exposure of mothers to stressors during gestation or postnatal periods resulted in hypomethylation of hypothalamic CRF (Mueller and Bale 2008; Chen et al. 2012) and AVP promoters (Murgatroyd et al. 2009); both changes were associated with HPA hyperactivity and altered behavior when pups reached adulthood. There is also evidence for epigenetic regulation of enzymes involved in steroidogenesis (Martinez-Arguelles and Papadopoulos 2010). However, direct evidence for environmentally-induced modulation of such regulation, as was the case for maternal adversity and CRF/AVP expression, is lacking.

Upon release of GCs from the adrenals, the pervasive physiological and behavioral actions of GCs are largely dependent upon sensitivity of target tissues (Sapolsky et al. 2000; Martin et al. 2016a), namely GC and mineralocorticoid (MR) receptor expression. Most available evidence for epigenetic modulation of HPA plasticity pertains to epigenetic modifications to GR (Weaver et al. 2004; Zhang et al. 2013b). Such effects are not altogether surprising considering the pivotal role of GR in coordinating physiological/behavioral responses to stressors and the resolution of stress responses (Sapolsky et al. 2000). For example, in rats, maternal dietary protein restriction resulted in hypomethylation of the hepatic GR promoter and a metabolic phenotype characterized by increased capacity for gluconeogenesis in offspring once they reached adulthood (Lillycrop et al. 2007). Within the hippocampus, the major site of GC negative feedback (i.e., the process by which release of GCs is ultimately reduced), numerous studies have found evidence for epigenetic regulation of GR. Among the most well-known examples, Liu et al. (1997) and Weaver et al. (2004) linked the impacts of maternal care and offspring behavior to epigenetic programming of the HPA axis of offspring. In rats, high maternal care (e.g., licking and grooming) within the first week of life was associated with long-term hypomethylation within the hippocampal GR promoter, reduced plasma ACTH, and CORT release in response to a restraint stressor, enhanced negative feedback sensitivity, decreased hypothalamic expression of CRF, and reduced anxiety-like behavior (Liu et al. 1997; Weaver et al. 2004). Taken together, these studies reveal that not only can the environment cause stable alterations in GC regulation via developmentally-induced epigenetic modifications, but they also indicate that such changes can influence the capacity for HPA flexibility and thus the extent to which GCs might affect phenotypes later in life.

Defining epigenetic potential

We define epigenetic potential as the capacity for environmentally-induced phenotypic change (i.e., plasticity) via epigenetic modifications to relevant genomic elements. The concept of epigenetic potential is relevant to many physiological pathways, but here we focus on epigenetic potential in the HPA axis because of its potentially important role in persistence at range-edges. An important aspect epigenetic potential is that it conveys well that promoter methylation and other particular forms of epigenetic variation set the boundaries within which HPA plasticity/flexibility can fluctuate. Epigenetic potential thus captures that fact that some epigenetic factors can capacitate latent physiological flexibility much as heat-shock proteins capacitate the actions of many genes (Rutherford et al. 2007). We argue below in detail that such latent plasticity (i.e., plasticity only manifested under specific environmental conditions) probably plays a powerful role in the fine-tuning of organismal-wide phenotypic responses to various environments, including those experienced by organisms moving into previously unoccupied areas. Variation in epigenetic potential can be underlain by genetic and/or environmental variation. Similar to the types of epigenetic variation described by Richards (2006), we argue that variation in

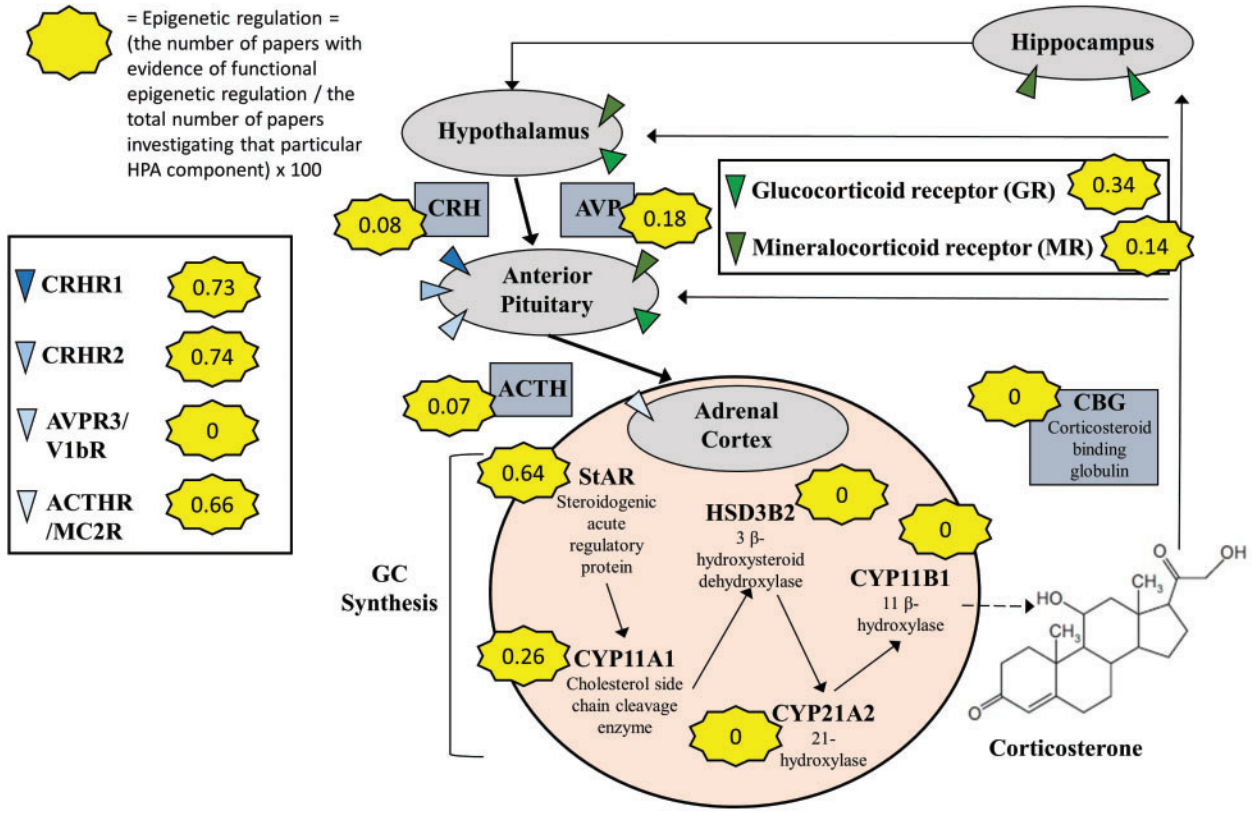

Fig. 1 Epigenetic regulation in the hypothalamic-adrenal-pituitary axis. The regulation of GCs by the HPA-axis is a complex process in which epigenetic mechanisms have the potential to influence multiple steps, from the upstream processes involved in initiating GC synthesis to the downstream actions of GCs on target tissues. A Web of Science search was conducted in December 2016 in order to reveal the components of the HPA-axis in which epigenetic variation have been observed and where epigenetic regulation most likely to occur. Each component of the HPA-axis was queried using search terms "epigenetic" and "component name" or "component abbreviation" or "associated gene" (for exact search terms see Supplementary Table S1). After filtering out document types besides peer-reviewed primary articles, studies were then sorted into categories based on content. Review or non-relevant papers were notated, as were studies that investigated epigenetic marks but found no significant patterns or relevance to functionality (i.e., gene expression, effects on behavior, etc.). Articles that reported functional impacts of epigenetic marks were categorized by mechanism (DNA methylation, histone modification, or other). Numbers in star burst-symbols denote epigenetic regulation within each HPA component, which is calculated as: (the number of papers with evidence of functional epigenetic regulation/the total number of papers investigating that particular HPA component) × 100. See Supplementary Table S2 for additional information.

epigenetic potential can range along a gradient from complete dependence on genetic variation (e.g., obligatory, Type 1), semi-dependence on genetic variation (e.g., facilitated, Type 2), or independent of genetic variation (e.g., pure, Type 3). Below, we provide examples from the literature to demonstrate several ways in which variation in epigenetic potential may arise and discuss their relevance for facilitating success in novel environments.

Genetically, epigenetic potential could be encoded (among other places) via sequence variation in (1) the exons of genes encoding enzymes that establish and maintain epigenetic marks, or (2) regulatory regions (e.g., promoters, enhancers) of the genome. First, organisms require the coordinated efforts of several enzymes to establish, maintain, and/or remove epigenetic marks from the genome as cells differentiate and organisms develop. Among the most commonly studied of these enzymes are the DNA methyltransferases (DNMTs), which catalyze the transfer of a methyl group to specific sites on DNA (Morris and Monteggia 2014). In vertebrates, the three main DNMTs are DNMT1, which primarily acts as a housekeeper to maintain methylation patterns through mitosis (but see Fatemi et al. 2002 for evidence of *de novo* methyltransferase capacity), and DNMT3a and DNMT3b, which are considered *de novo* DNMTs, capable of establishing methylation marks on previously unmethylated regions (Morris and Monteggia 2014). Given the importance of DNMTs as the molecular editors of the genomic blueprint, genetic variation within the genes encoding these enzymes can lead to functional variation in their catalytic activity (Potter et al. 2013;

Bjornsson 2015). In humans, for instance, genetic variation in DNMT3b was not only associated with altered DNA methylation patterns across 700 genes, but also with changes in function of several epigenetic enzymes involved in histone modification (Jin et al. 2008).

A second form of genetic variation in epigenetic potential includes variation within regulatory regions of the genome. In vertebrates, DNA methylation typically occurs at cytosines in the context of CpG dinucleotides (Schrey et al. 2013; Kilvitis et al. 2014). Such variation is quite common; within the human genome, there are >200,000 CpG single nucleotide polymorphisms (i.e., CpG-SNPs) (Shoemaker et al. 2010). Within regulatory regions (e.g., gene promoters, enhancers), the presence or absence of CpG sites would alter the substrate upon which epigenetic variation could occur. For example, CpG-SNPs within regulatory regions, particularly at transcription factor binding sites, can disrupt the binding capacity of transcription machinery (Zhi et al. 2013; Lemire et al. 2015) and thus alter gene expression. In a study by Zhi et al. (2013), >80% of CpG-SNPs surveyed from human T-cells were methylation quantitative trait loci (meQTL), and these SNPs accounted for nearly two-thirds of the strongest meQTL signals within T-cells. There is increasing evidence to suggest that not only do CpG-SNPs affect the potential for methylation at that particular CpG site, they also can influence methylation distal (*trans*) to CpG sites (Zhi et al. 2013; Lemire et al. 2015). Many naturally-occurring DNMTs and CpG-SNPs (and more complex genetic forms of epigenetic potential) could await discovery.

In addition to the above forms of epigenetic potential, akin to Type 1 epigenetic variation sensu Richards (2006), epigenetic potential is likely responsive to the environment. Most such forms of epigenetic potential will arise in early life, when cells have differentiated little and thus the phenotype has the greatest potential to be canalized into various forms (West-Eberhard 2003; Martin et al. 2011). Such critical periods of development are widespread (West-Eberhard 2003), and increasing evidence suggests that early-life experiences might enduringly alter epigenetic potential (Richards 2006). For example, prenatal or postnatal exposure to certain environmental toxicants has enduring, stable effects on the expression of several epigenetic regulatory proteins (Kundakovic et al. 2013; Schneider et al. 2013). In rats, dietary exposure to lead (Pb) during the prenatal and postnatal periods was associated with altered hippocampal protein expression of DNMT1, DNMT3a, and methyl-cytosine binding protein 2 (MeCP2) (Schneider et al. 2013), a protein that specifically binds to methylated DNA and recruits histone deacetylases (HDACs) to repress gene transcription (Jones et al. 1998). Moreover, prenatal rats exposed to environmentally-relevant doses of bisphenol A (BPA) had differential mRNA expression of DNMT1 and DNMT3a in the prefrontal cortex, hypothalamus, and hippocampus (Kundakovic et al. 2013). Interestingly, both of these studies found sex-specific and dose-dependent differences in the directionality of responses (i.e., up- or down-regulation), suggesting that the developmental programming of epigenetic potential can be fine-tuned contingent on sex as well as individual experience. In this way, variation in maternal exposure to toxicants can lead to the stable inhibition (e.g., via reduced expression of DNMTs) or enhancement (e.g., via increased expression of DNMTs) of epigenetic potential in her adult offspring.

Maternal-offspring interactions can also have lasting effects on epigenetic potential. For example, low maternal licking and grooming within the first week of life in rats was linked to increased hippocampal expression of DNMT1 in offspring in adulthood (Zhang et al. 2010). Maternal separation during the perinatal period in rats was also associated with promoter hypermethylation and reduced expression of *MeCP2* in the germ cells of male F1 offspring (Franklin et al. 2010). Furthermore, when investigating the transmissibility of these epigenetic marks across generations, the authors found that *MeCP2* methylation and expression were maintained in the germ cells of F2 males and the brain (cortex) of female F2 progeny (Franklin et al. 2010). While transgenerational epigenetic inheritance cannot be inferred without screening the epigenetic profiles of the male F3 generation (Skinner 2008; Skinner et al. 2010), studies such as this one, demonstrating multigenerational inheritance of epigenetic marks, suggest the exciting possibility of enduring, yet non-genetic, inheritance of epigenetic potential (Weaver et al. 2004).

Beyond occurrences in development, variation in epigenetic potential can also be influenced in adulthood by environmental factors. One of the best-studied examples entails modulation of the epigenome through diet. S-Adenosylmethionine (SAM) is the universal methyl-donor for histone and DNMTs, and its synthesis in the methionine cycle is facilitated by several dietary precursors (e.g., folate, methionine, choline, betaine, and vitamins B_2, B_6, and B_{12}) (Zhang 2015). For example, vitamins B_2, B_6, and B_{12} are key cofactors required for the synthesis of methionine, a direct precursor of SAM

(Zhang 2015). Thus, dietary deficiencies of methyl-donors directly influence the net synthesis of SAM, which has been associated with global DNA hypomethylation in rodents (Zhang 2015). In addition to regulating intracellular SAM, several dietary compounds can directly affect DNMT activity. For example, tea polyphenols (e.g., catechin) and genestein (found in soybeans) inhibit human DNMT1 activity (Fang et al. 2007; Zhang 2015). Moreover in humans, folic acid deficiency resulted in a ~50% decrease in DNMT1 expression and a concomitant 80% increase in DNMT3a expression in certain colorectal cancer cell lines (Farias et al. 2015). These studies strongly suggest that variation in the consumption of certain diet items could have profound effects on epigenetic potential, either via the modulation of methyl-donor bioavailability or the regulation of DNMT activity. Of course, diet is among the most likely factors to vary as organisms colonize new areas (Liebl and Martin 2014), implicating diet as a major factor whereby epigenetic potential mediates the outcomes of range expansions. Moreover, diet might represent a key environmental factor that could instigate a purely environmental, yet heritable, form of epigenetic potential mentioned earlier (Type 3, Richards 2006).

GCs, PRNs and, epigenetic potential in range expansions

As discussed above, GCs play an important role in mediating organismal performance due to their ability to coordinate diverse physiological and/or behavioral processes (Martin et al. 2011; Cohen et al. 2012; Martin and Cohen 2014; Martin et al. 2016b). Because of their capacity to influence multiple levels and aspects of organismal phenotype, GCs (along with other molecules) have been referred to as integrators (Martin et al. 2011; Cohen et al. 2012; Martin and Cohen 2014). Within the context PRNs, a framework recently proposed to represent whole-organism regulatory networks that link genetic and phenotypic variation (Martin et al. 2011; Cohen et al. 2012), GCs and their respective regulatory components (Fig. 1) resemble "hubs", or "central nodes", with higher than average connectivity with other nodes in PRNs including hubs of other subnetworks, such as those involved in immune function or energy metabolism (Cohen et al. 2012; Martin and Cohen 2014). This portrayal of the HPA is similar to the portrayal of master regulatory genes within gene regulatory networks, and "date hubs" for key proteins within protein-protein interaction networks (Wagner et al. 2007). PRN connectivity, then, represents the regulatory relationships among the HPA and other physiological nodes (Cohen et al. 2012; Martin and Cohen 2014); what sets apart date hubs, master regulatory genes, and physiological integrators is that links between these particular molecules and other nodes are exceptionally high. Whereas there are important differences between the roles of date hubs and integrators (e.g., the functions of one are predominantly intra-cellular whereas the other is organismal), such differences are beyond the scope of the focus of the article, epigenetic potential. Nevertheless, we believe that consideration of HPA elements as integrators within PRNs can help us understand how individual variation at the genetic/molecular level (including epigenetic potential) mediates variation at the whole-organism level, which we elucidate below.

PRNs and integrators therein have important properties that can affect epigenetic potential. First, PRNs have structure such that the configuration of PRN components and/or the strength/organization of these regulatory relationships vary among species, populations, and genotypes (Cohen et al. 2012). In other words, connectivity and other PRN traits vary contingent on evolutionary relatedness; closely related species should have similar PRNs and related genotypes should differ minimally in terms of various states that PRNs can take. Indeed for all genotypes, PRN structures are comprised of many states that are plastic in the sense of context-specific changes in network architecture (Cohen et al. 2012; Martin and Cohen 2014). As depicted in Fig. 2, we expect that epigenetic potential reveals and masks various PRN states, with concomitant changes in PRN connectivity and other networks traits underlying phenotypic adjustments in response to environmental factors. For range expansions in particular, shifts in PRN state (i.e., PRN plasticity; Martin et al. 2016b) should be more important than changes in PRN structure, as such shifts would allow genotypes to adjust more quickly to novel conditions than genetic mutations. Although this hypothesis has not yet been tested empirically, epigenetic mechanisms can alter GC regulation (and hence PRN state) in many ways (Fig. 1).

Consider a hypothetical example in which a newly established range-edge population is comprised of genotypes that vary in epigenetic potential (Fig. 2). At birth, variation in epigenetic potential among genotypes could unmask PRN states, altering the capacity for HPA regulatory flexibility throughout life. In other words, genetic variation in epigenetic potential could dictate the upper and/or lower limits of an individual's homeostatic range/reactive scope

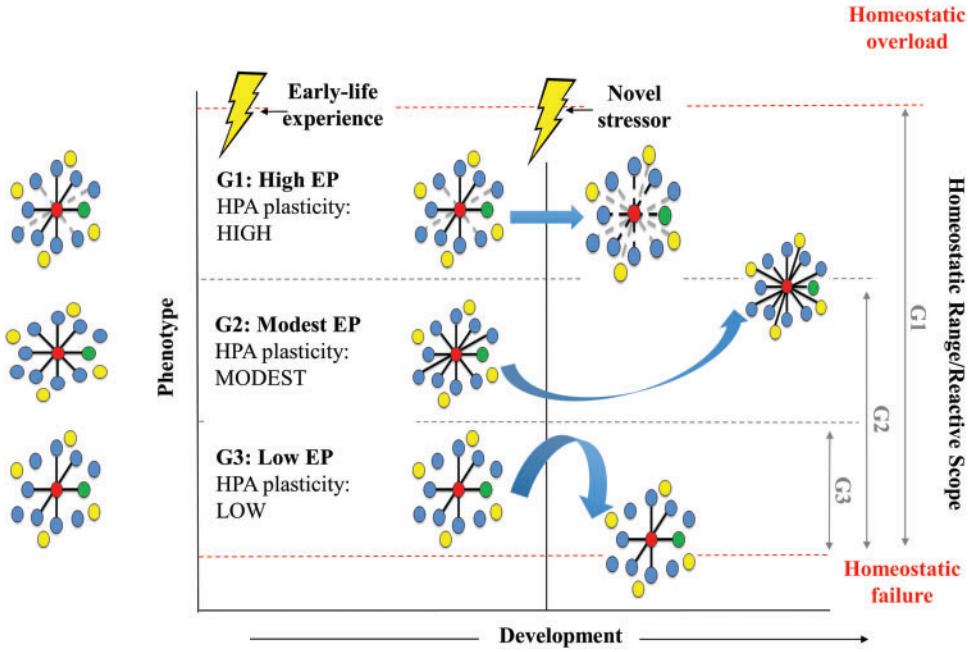

Fig. 2 Epigenetic potential as a mediator of plasticity in PRNs, and hence range-expansion success. In a hypothetical, newly established range-edge population, individuals (genotypes, G1–3) will vary in PRN state (due to plasticity) and structure (due to genes or enduring epigenetic marks) (e.g., connectivity). Some PRN structures (G3) have limited capacity for engaging in and stopping cross-talk (plasticity mediated via connectivity; lines among circles) between PRN hubs (e.g., aspects of the HPA—central circles) and other subnetworks (peripheral circles) and hubs. However, other individuals (G1) have high epigenetic potential and hence a strong propensity for plasticity in PRN states including reversibility (dashed lines). Such genetic variation in epigenetic potential could influence organismal responses to stressors via the impacts of epigenetic marks on HPA regulatory plasticity (e.g. individual variation in homeostatic range/reactive scope—Romero et al. 2009). However, some such variation probably is unmasked via developmental plasticity such as by exposure to an early-life stressor (left lightning bolt; early-life experience). In these cases, connectivity among PRN components in genotypes with low epigenetic potential may remain unchanged (G3). In contrast, the PRN state of genotypes with modest or high epigenetic potential (G1 and 2) would be capable of responding plastically to the early-life stressor to varying degrees (formation of new lines between circles). In individuals with modest epigenetic potential, early-life stressors might alter PRN connectivity similarly to individuals with high epigenetic potential, however, low expression of genes encoding epigenetic modifying enzymes and/or dietary restriction of methyl-donors could stabilize connectivity within PRNs (i.e., solid lines), at least compared genotypes with high epigenetic potential here facilitating reversibility in connectivity (i.e., dashed lines). Contingent on further experience, environmental alterations to epigenetic potential (via diet or exposure other stressors—right lightning bolt) might further modify PRN state. Here, low epigenetic potential in G3 and the resultant limitations to PRN plasticity could result in under-exuberant responses of the HPA to novel stressors (e.g., homeostatic failure; lower dashed line—Romero et al. 2009) whereas modest epigenetic potential for G2 might underlie over-exuberant responses to stressors (e.g., homeostatic overload; upper dashed line—Romero et al. 2009). For G1, high epigenetic potential might maximize phenotypic integration and de-integration (as stressors arise and subside or are surmounted/avoided) via the reversibility of edge formation among PRN subnetworks.

(Romero et al. 2009); epigenetic potential probably titrates HPA plasticity based on developmental experience. For example, in genotypes with low epigenetic potential (G3; Fig. 2), connectivity among HPA nodes, and other PRN nodes would be limited, constraining HPA flexibility in response to an early life stressor. In contrast, for genotypes with modest (G2; Fig. 2) or high epigenetic potential (G1; Fig. 2), epigenetically-mediated alterations to PRN state could allow PRNs to recruit and/or eliminate linkages with other subnetworks and nodes. In individuals with modest epigenetic potential (G2), exposure to an early life stressor might alter PRN state (i.e., connectivity; Fig. 2) modestly, and ultimately canalize edges among PRN nodes. For some genotypes (G1), however, exposure to the same early life stressor would only transiently alter PRN states, allowing for reversibility in PRN states, and thus greater HPA flexibility throughout life. In adulthood, for genotypes with low epigenetic potential, HPA plasticity would remain modest, here depicted as the inability to alter the PRN adequately in response to novel stressors (e.g., homeostatic failure—Romero et al. 2009). For genotypes with modest epigenetic potential, individuals might be unable to down-regulate GCs rapidly, because of a lack of reversibility, resulting in chronic stress (e.g., homeostatic overload—Romero et al. 2009).

In regards to high epigenetic potential, it is premature and likely untrue, in some cases, that such genotypes will always be at an advantage. First, high epigenetic potential, and thus greater HPA plasticity might be adaptive at range-edges at some stages of expansion. However, there is increasing evidence that the costs of plasticity could lead to dominance by genotypes with more modest epigenetic potential over time (Ghalambor et al. 2007; Huang et al. 2015). One hypothesis proposed by Huang et al. (2015) suggests that the presence or absence of stressors at the range-edge can influence the costs/benefits of plasticity, and thus the extent to which such plasticity is adaptive or maladaptive. For instance, exposure to novel stressors, such as novel enemies, may increase the costs and reduce the benefits of plasticity (via reallocation of resources towards defense), resulting in plasticity that is maladaptive (Huang et al. 2015). Alternatively, relief from stress (e.g., via natural enemy release) may reduce the costs and increase the benefits of plasticity, in which case plasticity would be adaptive (Huang et al. 2015). While there are no data as of yet on the costs and benefits of epigenetic potential in range expansions, we acknowledge the value of such research and particularly its evolutionary insight.

A second reason to be cautious about what forms of epigenetic potential will endure at range-edges involves the purely environmental forms of epigenetic potential (Type 3 variation *sensu* Richards 2006) mentioned above. Diet, novel pathogen exposure, or other experiences unique to range-edges might commonly lead to forms of plasticity that become increasingly maladaptive as populations become established (Richards 2006; Ledon-Rettig et al. 2013). What food parents consume or what infections they experience are apt to change over time; if such epigenetic marks are enduringly passed across generations, offspring would suffer as they would manifest phenotypes inappropriate for current conditions. Similar outcomes could occur too for Type 2 forms of epigenetic potential (i.e., G × E), particularly because there are typically more ways to produce non-functional phenotypes than there are to produce functional ones.

Future directions

Above we argued that epigenetic potential and its mediation of phenotypic plasticity via alterations to PRN states affect vertebrate range expansion success. Whereas some aspects of the concept of epigenetic potential have been alluded to previously (a Web of Science search for "epigenetic potential" on March 8, 2017 returned 17 hits), to our knowledge, this article is among the first to define the term explicitly in regards to its genetic underpinnings, its physiological functions, and its prospective ecological and evolutionary consequences. Given the infancy of epigenetic potential as a concept, we use the remainder of our article to highlight some promising avenues for future research.

In Fig. 1, our primary goal was to reveal where in the HPA axis the most epigenetic variation is known to occur. This figure thus depicts but a small part of the epigenetic potential we discussed earlier. However, it is does draw attention to the parts of the HPA that so far seem to harbor some epigenetic potential. A Web of Science search (conducted in December 2016, see Supplementary Table S1 for search terms) revealed substantial epigenetic modulation throughout the HPA. Particular HPA aspects, though, were disproportionally more likely than others to be altered by epigenetic mechanisms (Fig. 1; Supplementary Table S2). To try to account for possible biases in research effort that might affect the number of epigenetic marks described for each HPA aspect, we quantified the number of studies reporting epigenetic effects within a particular HPA component and adjusted that count by the total number of published primary research studies on that particular HPA component. In Fig. 1 and Supplementary Table S2, we report this ratio. Although most available data came from laboratory rodents, which are not the most evolutionarily-relevant organisms, four of the top five HPA components most likely to be epigenetically regulated were receptors. The only non-receptor component was the gene encoding steroidogenic acute regulatory protein (StAR or STARD1). StAR is the rate-limiting step in the synthesis of most major steroid hormones, including GCs (Christenson and Strauss 2001). Among the top four receptors, rankings (highest to lowest) were as follows: CRH receptor 2 (CRHR2), CRH receptor 1 (CRHR1), ACTH receptor (ACTHR or MCR2), and GC receptor (GR).

These results suggest that epigenetic potential for HPA regulatory plasticity might be most extensive for receptors. In a sense, this outcome is unsurprising given that receptors are particularly important for the initiation of the stress response, distal actions at target tissues, and negative feedback. We also note that the evidence for epigenetic regulation was highest among all factors we considered for GC response elements (GREs). We chose to exclude GREs from the rankings in the table, however, because they occur across the genome, are harder to enumerate, and thus hard to compare to our other estimates. Overall, given the rarity of studies for some HPA

components, we are reluctant to conclude that our crude estimates capture epigenetic potential in the HPA. Nonetheless, we hope it motivates other, more direct, efforts to measure epigenetic potential. Loci with high epigenetic potential could be particularly important targets for environmental modulation of organismal-wide plasticity and selection.

A second critical research venture involving epigenetic potential and the HPA would evaluate directly the value of the PRN construct. For instance, using transcriptomic approaches, one could determine: (1) how HPA manipulations influence variation or plasticity in relevant phenotypic traits; (2) the extent to which observed phenotypic integration/de-integration is associated with changes in PRN traits; and (3) whether PRN plasticity via manipulation of GC synthesis or negative feedback is associated with epigenetic variation. An alternative approach would be to administer drugs, such as 5-aza-2′-deoxycytidine or trichostatin A (e.g., Weaver et al. 2004; 2006), or to manipulate dietary intake of methyl-donors (e.g., Waterland and Jirtle 2004), both of which alter epigenetic marks. Again, the use of transcriptomic tools could reveal whether such manipulations influences GC regulatory plasticity and if so, how this plasticity is associated with PRN states (Martin et al. 2011; Cohen et al. 2012; Martin and Cohen 2014).

Lastly, it will be useful to identify additional factors that contribute to variation in epigenetic potential. Whereas we focused primarily on how epigenetic potential acts as a source of HPA regulatory plasticity, there is some evidence that GCs can influence epigenetic potential. For example, dexamethasone (DEX) treatment reduced (human) natural killer (NK) cell cytokine expression in a dose-dependent manner, and was associated with increased cytokine promoter-specific histone deacetylation. Further, these DEX effects were reversible upon treatment with the histone deacetylase inhibitor, trichostatin A (Krukowski et al. 2011). In another study on rats, prenatal exposure to lipopolysaccharide (LPS), an immunogenic component of Gram-negative bacterial cell walls, had enduring effects on DNMT1 and DNMT3b expression within the adrenal cortex (Wang et al. 2017).

Conclusion

Given increases in the occurrence of natural and especially anthropogenically-mediated species' range shifts, it is becoming increasingly important to understand the mechanisms that facilitate whole-organism performance and thus range expansions. Here, we highlighted molecular epigenetic potential in the HPA as a plausibly important form of genotype × environment (G×E) (and potentially individual × environment (I×E) (Nussey et al. 2007)) interaction. Epigenetic potential—particularly when physiological integrators are involved—allows not only for rapid phenotypic adjustments in response to salient environmental cues, but also may act as an additional source of variation for overcoming genetic paradoxes. We therefore believe that epigenetic potential in HPA plasticity warrants extensive investigation in various native and non-native range expansions as well as other contexts in which populations are being forced to adjust to rapid environmental change.

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Supplementary data

Supplementary data available at *ICB* online.

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