Living in the Now: Physiological Mechanisms to Tolerate a Rapidly Changing Environment

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Key Words

ocean acidification, environmental stress, climate warming, global warming, acclimatization

Abstract

Rising atmospheric carbon dioxide has resulted in scientific projections of changes in global temperatures, climate in general, and surface seawater chemistry. Although the consequences to ecosystems and communities of metazoans are only beginning to be revealed, a key to forecasting expected changes in animal communities is an understanding of species' vulnerability to a changing environment. For example, environmental stressors may affect a particular species by driving that organism outside a tolerance window, by altering the costs of metabolic processes under the new conditions, or by changing patterns of development and reproduction. Implicit in all these examples is the foundational understanding of physiological mechanisms and how a particular environmental driver (e.g., temperature and ocean acidification) will be transduced through the animal to alter tolerances and performance. In this review, we highlight examples of mechanisms, focusing on those underlying physiological plasticity, that operate in contemporary organisms as a means to consider physiological responses that are available to organisms in the future.

INTRODUCTION

GCC: global climate change

It is becoming increasingly clear that comparative animal physiologists have a place at the table in the pursuit to understand how global climate change (GCC) will affect organisms (1–4). From a broad perspective, there are three main response options for organisms facing GCC: (*a*) Species may disperse to more hospitable habitats, (*b*) phenotypic and physiological plasticity may allow species to tolerate the new conditions, or (*c*) they may adapt to the new conditions through genetic change via the process of evolution (e.g., 5). Pivotal to our ability to forecast the impacts of GCC is the second category, physiological plasticity: To what degree can the phenotype of any given organism "stretch" to accommodate the unprecedented rates of environmental change that are expected in the next 100 years (see sidebar: Physical Drivers of Global Climate Change)? In this review—the "living in the now" perspective in the trio of reviews on climate change—our focus is on the mechanisms that could potentially operate to offset the deleterious impact of GCC in extant populations and, additionally, on proposing areas that are rich for future investigation. With a focus on various physical drivers, we highlight (*a*) mechanisms that species can use to adjust their physiology to changes in the environment; (*b*) how these mechanisms might contribute to compensatory responses to GCC drivers; and (*c*) trade-offs regarding these mechanisms, especially in a multiple stressor situation expected in GCC scenarios.

PHYSICAL DRIVERS OF GLOBAL CLIMATE CHANGE

***CO_2 Emissions* (138, 148)**

- Atmospheric CO_2 concentration has risen 100 ppm since the Industrial Revolution
- Present globally averaged CO_2 concentration: 385 ppm CO_2
- Projected CO_2 equivalents for 2100: 600 (B1) to 1550 (A1FI) ppm CO_2
- Annual CO_2 growth rate (1995–2005): 1.9 ppm·year^{-1}

***Climate Warming* (138, 149, 150)**

- Over the past century, global mean surface temperature has risen by 0.74°C (1906–2005)
- Projected to rise by 2–4.5°C (mean B1 = +1.8°C, A1FI = +4°C) by 2100—the consensus is still most likely 3°C. Approximately 50% of the warming that will be experienced in the next 20 years will be due to climate change that is already committed
- Warming rate of this century is projected to be five times the rate that was documented in the previous century (twentieth century = 0.6°C and twenty-first century = 3°C)
- Significantly faster warming rates over land than ocean in the past two decades (approximately 0.27°C versus 0.13°C)
- "Very likely" that heat waves will be more intense, more frequent, and longer lasting

***Ocean Acidification* (138, 148)**

- Since 1750, there has been an average decrease in ocean pH of 0.1 units
- Projected CO_2-driven ocean acidification for 2100: decrease in pH of 0.14–0.35 units
- Within the past 20 years, there has been an average decrease in ocean pH of 0.02 units·decade^{-1}

Overview

Comparative physiology has traditionally examined the tolerance of organisms to environmental change and the underlying mechanisms that define the limits or thresholds of physiological capacity. Although these thresholds have been captured historically in ways ranging from reactions norms (6) to tolerance polygons (7), the information they convey is the same: Animals have ranges of environmental conditions in which performance is maximized as well as thresholds beyond which performance fails and tolerance becomes time-limited (**Figure 1**). Knowing where an animal exists today within its "tolerance thresholds" and to what degree predicted climate change will shift this position may allow us to assess which species are vulnerable. In this review, we revisit the idea of tolerance windows, with an eye on GCC and the physical drivers that are predicted with certainty to change by the year 2100 (see sidebar: Physical Drivers of Global Climate Change). The unprecedented rate of climate change prevents a reliance on

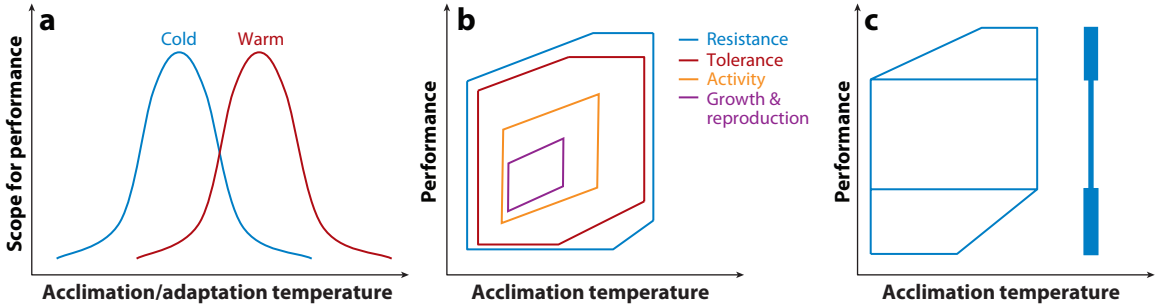

Figure 1

Temperature effects on physiological performance. (*a*) A clear link exists between the range of environmental change that characterizes an animal's natural environment and the range of conditions that the animal can tolerate. Temperature acclimation or adaptation can shift the position of the thermal window along the temperature scale to a limited extent such that the animal's scope for performance, or response curve, is more suited to its environment. (*b*) The temperature thresholds for long-term performance requiring growth and reproduction are much narrower than those required simply for survival over acute (resistance) to chronic (tolerance) timescales. (*c*) An animal's tolerance is made up of an intrinsic or acclimation temperature-independent tolerance component (*narrow bar*) as well as an acquired or acclimation temperature-dependent tolerance component (*wide bar*).

adaptation as a strategy for many organisms [8–12; but see the review by Feder et al. (13) in this volume]. Likewise, for many organisms with longer generation times, already existing populations will experience these novel future environments. Therefore, critical to forecasting how contemporary organisms will fare in the face of GCC is understanding (*a*) the physiological sensitivity of organisms to the physical drivers of climate change (e.g., temperature and ocean acidification) and (*b*) the physiological capacity of these organisms to buffer additional environmental change. Although we focus on mechanisms that underlie physiological plasticity, or acclimation capacity, from the molecular to the organismal level (e.g., 14), where possible we comment on the degree of genetic change necessary for adaptation to play a role in buffering the effects of GCC. Finally, given the compendious literature on these topics, we have chosen to focus on studies that specifically parameterize the effects of climate change.

ENVIRONMENTAL TEMPERATURE

Temperature is a primary physical driver setting limits on species' abundance and distribution (15). As a result, climate change stands to restructure ecosystems as temperature is transduced through organismal tolerances to influence their ecological distributions. Indeed, evidence from polar, temperate, and tropical ecosystems indicates that temperature-linked shifts in organismal distribution have already occurred in response to a changing climate (16–18). However, the physiological mechanisms underlying these trends remain unclear, although these connections will provide important insight (2). In fact, the precise physiological and biochemical mechanisms that define the upper and lower thermal tolerance limits are often still unknown, despite our extensive understanding of how temperature affects organismal physiology and biochemistry. To predict how climate change will affect an organism's physiology in the future, we start by outlining our understanding of how environmental conditions (i.e., the thermal histories of organisms) have shaped the physiology of today's organisms. We start by briefly reviewing the mechanisms that underlie the thermal sensitivity of organisms, while directing readers to the numerous reviews and studies that elucidate these mechanisms. We then synthesize existing data regarding how close organisms are living to their thermal limits and whether the increases in global temperatures that are predicted to occur over the next century will be enough to have significant

K_{cat}: catalytic rate constant

K_m: Michaelis-Menton constant

effects on organismal physiology and, ultimately, species distribution and abundance. We exemplify these themes with ectothermic organisms, which both are major constituents of marine and terrestrial communities and have a limited ability to regulate their internal body temperature (and accordingly are vulnerable to GCC). Obviously, forecasting the response of animals to GCC drivers must encompass more than just physiological sensitivity, e.g., the animal's ability to buffer the effects of climate change through behavior. For example, terrestrial cold-blooded ectotherms might not be able to stay cool enough through behavioral thermoregulation due to indirect effects of changes in vegetation cover (19).

Integrative comparative physiology has been informative for understanding how subtle changes in thermal environments have affected physiological sensitivities to temperature through differences in adaptive capacities to buffer the effects of temperature change (20). This research provides a good foundation for understanding both the evolutionary and acclimatory adjustments that can extend the thermal limits of organisms. Apart from some work on the microevolutionary processes in *Drosophila* (21, 22), information on the heritability of thermal traits is limited, especially for organisms with comparatively long generation times. Whereas adaptive rescue of populations from GCC is therefore possible, it is highly unlikely for many. Given the rate of warming that is expected (see sidebar: Physical Drivers of Global Climate Change), the capacity of contemporary organisms to defend cellular homeostasis through acclimatory adjustments seems more likely to be critical to their ability to buffer the effects of climate warming. Although much of the research examining the mechanisms that set thermal optima and thresholds/limits has focused on timescales of days to weeks and not those of years, these mechanisms do provide us with good indices of potential limits to the capacity of these biochemical mechanisms to "flex" over the decades that will constitute this natural acclimatization experiment of committed climate change.

Biochemical Adaptations to Temperature/Cellular-Level Processes

Thermal stability of proteins. At environmentally relevant temperatures, enzymes must be sufficiently stable to maintain a functional conformation for proper substrate and cofactor binding but must also be sufficiently flexible to undergo the conformational changes required to catalyze a reaction and support metabolic flux (see Reference 23 for a review). Over evolutionary timescales, amino acid substitutions have resulted in adaptive changes in stability and kinetic properties of enzymes to yield orthologous enzymes that function efficiently under specific habitat temperatures (24). This adaptation affects both the catalytic rate constant of the reaction (K_{cat}) and the temperature dependency of substrate and cofactor affinity (K_m). Over shorter timescales, thermal acclimation cannot produce a new ortholog with more appropriate kinetic properties. However, in addition to changing protein concentration, thermal acclimation in some cases can change the isoform of a specific protein that is expressed such that organisms can "switch" isoforms to one that is better suited to a particular thermal environment (25). Over the timescales relevant to GCC, these data suggest that most animals will rely on protein stability mechanisms already in place. The K_m of a particular ortholog is known to increase with increasing temperature, corresponding to a decrease in substrate affinity. Orthologs of warm-adapted species have K_m values that are less sensitive to temperature and therefore undergo a less steep increase in K_m with increasing temperature. Eventually, temperature increases will exceed the intrinsic thermal stability of the protein, resulting in dysfunction of the enzyme. The temperature thresholds for loss in function can be within the upper range of the physiological temperatures experienced by a particular species (e.g., see 26). Finally, recent studies have provided some insight into how much adaptive genetic change is needed to acquire a new ortholog of a particular enzyme (27, 28); however, the time

required for these types of amino acid substitutions is at a scale that dwarfs the decades that represent committed climate change.

Once environmental temperatures start to approach an organism's thermal limit, an organism's survival will depend on the capacity to effectively maintain or restore the integrity of the protein pool following a thermal perturbation. One well-characterized cellular defense mechanism is the heat shock response (HSR), which involves the induction of a highly conserved group of molecular chaperones, also known as heat shock proteins (Hsps), that are critical in the defense of protein homeostasis, the refolding of denatured proteins, and the breakdown and replacement of the proteins that are not repairable (see Reference 29 for a review). Much that is known of the functional significance of these proteins in natural populations of metazoans has come from work on *Drosophila* as well as that on intertidal ectotherms (29, 30). The utility of this response requires both the production of Hsps and the energy for Hsps to function properly. Recently, Anestis and colleagues (31) linked biochemical stress indicators with metabolic status to expand our understanding of the "systemic to molecular hierarchy of thermal limitation." Their study on the thermal limits of an intertidal mussel (*Modiolus barbatus*) provides some indirect but initial evidence of links between a decrease in aerobic capacity, as indicated by the activity of pyruvate kinase, and activation of the cellular stress response, as indicated by increased gene expression of a number of *hsps* and stress signaling pathways.

Membrane properties. Membranes play diverse and essential roles as physical barriers, controlling the transport of molecules, establishing ion gradients across cellular compartments, and acting in membrane-based cell signaling and synaptic transmission. Temperature change can disrupt membrane packing order, also known as membrane fluidity. Changes in membrane order can lead to changes in membrane-associated processes and eventually complete disruption of function; therefore, modulation of the lipid environment is a critical aspect of thermal adaptation. The defense of membrane order in the face of changes in environmental temperature, homeoviscous adaptation (HVA) (32), involves remodeling membrane lipids via changes in head group composition, acyl chain length, and saturation as well as changes in the cholesterol content of membranes (see Reference 33 for a review).

Organisms display considerable plasticity in membrane order over both spatial as well as temporal scales. Warm-adapted or warm-acclimated individuals have membranes that are more rigid than those of cold-adapted/-acclimated individuals to counteract the destabilizing effects of elevated temperature (34). Membrane order can also change rapidly. For example, membranes can be restructured in intertidal mussels within hours in response to temperature fluctuations during the tidal cycle (35). Therefore, animals have some potential to respond to rapid weather events, but the capacity to remodel their membranes is dependent on recent exposure history (35). Arrhenius break temperatures (ABTs) in mitochondrial respiration correlate strongly with membrane properties, as measured using a technique of fluorescence polarization, providing good estimates of what temperature results in loss of membrane stability (34). Such data show that the ABTs of mitochondrial respiration in warm-adapted organisms are closer to their maximum habitat temperature than in cold-adapted animals, suggesting that warm-adapted organisms are already existing close to their thermal limits. In fact, membrane dysfunction can occur at temperatures below ABTs of mitochondrial respiration when membranes become "leaky" and ions rapidly permeate a now ineffective physical barrier. Organisms must then be able to restore transmembrane ion gradients, which involves the energy-dependent sodium pump, Na^+/K^+-ATPase, as well as remodel their membranes, to survive such temperature increase.

HSR: heat shock response

Hsp: heat shock protein

HVA: homeoviscous adaptation

ABT: Arrhenius break temperature

OLTT: oxygen-limited thermal tolerance

T_{opt}: thermal optimum

Molecular Adaptations/ Molecular-Level Processes

Organisms adjust gene expression to achieve physiological plasticity in response to a physical driver such as temperature. Functional genomics approaches have been applied to model systems (e.g., 36, 37), in laboratory studies with climate change–relevant manipulations using nonmodel organisms (38–41), and in the field (42, 43). This work reveals the transcriptomic response of organisms as they are undergoing variations in temperature. Transcriptomic analysis may reveal changes in gene regulatory networks that disclose the potential for plasticity in response to changing environmental factors (41, 44). Notably, a systems biology approach has been employed in the studies of stress responses in plants (45), and such an integrated approach may be very useful in the study of responses to thermal stressors in metazoans in a climate change context.

Flexibility in Performance/ Organismal-Level Processes

Although organisms are adapted to a wide range of environmental temperatures, maintenance of a narrow thermal window ought to minimize the costs associated with plasticity. The physiological mechanisms that extend thermal windows are energetically demanding, and this cost is met at the expense of other critical functions such as growth and reproduction. Although the various adjustments to temperature reviewed above contribute to survival during a thermal perturbation, the overall resilience of a species in the face of GCC also involves overall organismal fitness and the "cost of living" in a rapidly changing environment.

The temperature dependency of aerobic capacity can elucidate an animal's physiological sensitivity to GCC. According to the oxygen-limited thermal tolerance (OLTT) hypothesis, the inability of ventilatory and circulatory delivery of oxygen to meet the increased oxygen demand caused by increased temperature is a proposed mechanism limiting performance at high temperatures in ectotherms (see Reference 46 for a review). This reduced capacity to perform aerobically at high temperatures has repercussions for many aspects of fitness such as activity, growth, and reproduction and, ultimately, could limit an organism's thermal niche and geographical expansion (47). Linking thermal performance breadth as well as optimal performance temperature of an organism to its ecology (48) in the context of a warming climate will be a useful predictive tool for understanding the effects of GCC. Studies have addressed these linkages with an eye to GCC and provided excellent insight into what aspects of environmental temperature (e.g., mean ambient temperature, extreme thermal events, and rates of warming) are ecologically relevant to organismal fitness.

Mean ambient temperature. Farrell and colleagues (49) demonstrated a close match between optimal temperature for maximum aerobic scope (T_{opt}) in Pacific sockeye salmon and the average river temperature encountered by the population during its spawning migration. Salmon population stocks of late spawners (e.g., Weaver Creek sockeye salmon in British Columbia, Canada) have already been shown phenologically to enter their natal streams earlier during warmer-than-average summers and, as a result, encounter water temperatures that are not optimal for intense exercise. In certain cases these stocks completely disappeared in such years, which the authors attribute to loss of aerobic scope (the difference of standard and maximum rates of oxygen consumption). Nilsson et al. (50) likewise showed that coral reef fishes of the Great Barrier Reef have greatly reduced aerobic scope at temperatures only a few degrees above summer mean temperatures. Furthermore, reef species differed in thermal sensitivity (i.e., two cardinalfish species are more sensitive to high temperature than are three damselfish species), highlighting the potential of GCC to affect community structure/ assemblages. From climate data and insect performance curves, Deutsch et al. (51) have derived simple but useful indices of how climate warming will affect insects along a

latitudinal gradient. Using an organism's mean habitat temperature (T_{hab}), its thermal optimum (T_{opt}), and its critical thermal maximum (CT_{max}), the authors define an organism's warming tolerance ($WT = CT_{max} - T_{hab}$) and thermal safety margin ($TSM = T_{opt} - T_{hab}$). An organism's WT and TSM will inform which species are currently vulnerable to GCC and, ultimately, which ecosystems are most vulnerable. This type of analysis is also under way in other systems. Huey and colleagues (52) have suggested that tropical forest lizards are especially vulnerable to GCC because of their small TSM, in part due to their inability to access thermal refugia (19) that could lower their T_{hab}.

Time between extreme thermal events. Organisms that have undergone a thermal challenge require time to recover physiologically, and therefore the interval between extreme high temperature events will likely be an important determinant of a species' resilience in the face of GCC. According to the model of Donner et al. (53), corals' increase of their thermal tolerance by 1–1.5°C will postpone their vulnerability to bleaching events by ~30–50 years. These authors acknowledge, however, that certain species and growth forms will be able to increase their tolerance more effectively than others, and as a result coral community structure may still change drastically.

Rate of warming. The rate of warming markedly affects thermal tolerance limits of organisms (e.g., 54, 55). In *Linepithema humile*, an invasive ant species, CT_{max} decreased 8°C when the warming rate was reduced from 0.5°C min^{-1} to 0.05°C min^{-1} (54). Peck and colleagues (55) investigated the effect of the warming rate on the survival of 14 species of Antarctic invertebrates; in all species, the upper temperature tolerance limit decreased substantially when the warming rate was decreased from 1°C day^{-1} to 1°C $week^{-1}$ to 1°C $month^{-1}$. When the warming rate was slowed to 1°C $month^{-1}$, thermal limits were found to be only 2–3°C above current summer mean temperatures. Furthermore, their empirical data project that the thermal limit of many of these organisms would be close to 1.3°C above current summer mean temperatures if warming is slowed to 1°C $year^{-1}$. At Rothera Station, the maximum summer temperature has already exceeded this threshold in some years. This work implies that previous studies may have inflated thermal tolerances by incorporating warming rates greater than those predicted for climate-induced warming over the next 90 years.

T_{hab}: mean habitat temperature

CT_{max}: critical thermal maximum

WT: warming tolerance

TSM: thermal safety margin

A role for symbioses. Organisms that form symbioses possess an additional mechanism of resistance to thermal stress associated with climate change: Namely, the physiological properties of the symbiont may influence the tolerance range of the holobiont. One of the best-known examples of this situation is the mutualistic symbioses formed by stony corals and photosynthetic dinoflagellates in the diverse genus *Symbiodinium*. Work on the thermotolerance of corals (e.g., 56, 57) suggests that the composition of the symbiont community affects the thermal sensitivity that is associated with and causes coral-bleaching events (10, 58, 59). Ongoing research has focused on whether corals can shuffle existing symbionts or switch symbionts (i.e., take up new clades from the environment) and thereby rapidly increase their thermotolerance.

With regard to symbiont shuffling, in a field transplant study, corals that changed their dominant symbiont type to Clade D, a well-known thermally tolerant variety of *Symbiodinium*, increased their thermotolerance by 1–1.5°C (60). In addition, observations from the field have documented that high temperatures are correlated with the distribution of *Symbiodinium* type in corals (61, 62) and that the symbiont type changed, and possibly conferred thermotolerance, during natural bleaching events (61, 63, 64). Overall, the experimental and observational evidence that symbiont shuffling is a mechanism by which some stony corals may acclimatize to climate change–related thermal stress is strong, although the mechanism that controls the

OA: ocean acidification

DIC: dissolved inorganic carbon

shuffling and winnowing of the symbionts is still unknown (59, 65, 66). When the process is modeled (67), i.e., when genetic or symbiont thermotolerance is allowed to vary, thermotolerance of the symbiont has a role in setting the thermotolerance of the holobiont. Notably, some corals seem incapable of symbiont shuffling; the massive corals in the genus *Porites* represent one of the most thermally tolerant stony corals, and they have a tight, seemingly exclusive association with a single type of *Symbiodinium* (68).

Consensus on relevant indicators of *Symbiodinium* diversity is still a work in progress (69–71), however, and thus how the symbiont can alter the performance of the holobiont in the face of changing environmental conditions is not completely resolved. Nonetheless, a salient feature of symbiont shuffling as a mechanism—initially proposed as a response to bleaching (72)—is that it may be more rapid than microevolution in increasing thermotolerance. Indeed, Harmon et al. (73) illustrated this rapidity in a recent study on pea aphids that contain bacterial endosymbionts that confer tolerance to a higher frequency of heat shocks.

OCEAN ACIDIFICATION

Ocean acidification (OA) has recently emerged as a major environmental factor that is associated with global climate change (74) and may have sweeping repercussions for marine ecosystems and their metazoan residents. Recent models that couple climate change and the ocean carbon cycle estimate decreases in ocean pH of 0.25 and 0.48 units at CO_2 stabilization levels of 550 and 1000 ppm, respectively (75, 76). This degree of ocean acidification is likely to reduce saturation levels for aragonite and calcite, two mineral forms of calcium carbonate that are crucial for calcifying marine organisms. Thus far, most research has focused on the biological effects of low pH and undersaturated waters on calcifying organisms (see References 74 and 77 for a review). These studies are sometimes criticized as not realistic in that they do not encompass the capacity for adaptation. Nonetheless, this important work demonstrates that, rate of evolution aside, ocean acidification will significantly affect the physiology of contemporary biota. The next phase of these studies will benefit from explorations of mechanisms (4) and the capacity for physiological plasticity, phenotypic plasticity, and microevolution to buffer these negative effects.

Calcification has been highlighted as one of the most vulnerable physiological processes in an OA scenario (78). Across a variety of calcifying taxa, most studies have demonstrated reduced calcification in response to increased pCO_2 and decreased concentrations of carbonate ions and reduced saturation states (summarized in Reference 74), although species-specific responses have shown variation in laboratory experiments (79–81). The majority of these OA-focused calcification studies have examined scleractinian corals and phytoplankton (77, 82). Laboratory experimentation on stony corals has shown a correlation between low concentrations of carbonate ions and a decline in calcification (83–85). For example, in the coral *Acropora eurystoma*, calcification declines 33% under conditions of low carbonate ions and low pH (85). Mechanistically, the decline in calcification is linked to the acidification-driven decrease in carbonate concentrations and not to the effects of seawater acidification on symbiont photosynthesis (84, 85). However, as processes, calcification and photosynthesis are in competition for DIC (dissolved inorganic carbon) in corals (86). Although the precise cellular mechanism that controls calcification in coral cells is unknown (87), and because calcification is a regulated process (88–90), as-yet-unrecognized compensatory mechanisms may exist.

The exact linkages among elevated CO_2, OA, and physiological dysfunction in the context of GCC need further study. Elevated CO_2 was originally assumed to be problematic because it reduces ocean pH and hence the physical availability of carbonate. This scenario is problematic. Carbonate itself is rarely transported across membranes (91–93) but rather

enters via diffusion of CO_2 or ion exchangers' transport of bicarbonate. Bicarbonate is at higher concentrations in CO_2-acidified water and therefore ought to increase calcification under OA if carbonation is the principal driver. Although a minority of studies report that elevated CO_2 does not affect or increases calcification, most studies report decreases in calcification (94). This variety of responses is unexpected if CO_3^{2-} is the driver. More likely the effect of elevated CO_2 or hypercapnia on cellular pathways, rather than calcification per se, is the key problem. This idea is consistent with the effects of elevated CO_2 on noncalcifying organisms, which show many similarities in their response to CO_2-acidified water, including decreases in metabolism and protein biosynthesis (95–97).

OA doubtless affects calcification greatly. The sensitivity of marine calcifiers to OA, however, is likely not directly related to the fact that they are calcifiers but more likely due to their low capacity for regulating acid-base status, particularly extracellular pH (for examples, see 98, 99). Because calcification itself results in the generation of a proton with the precipitation of $CaCO_3$ from Ca^{2+} and HCO_3^-, maintenance of acid-base status within the calcification compartment requires that this proton be pumped out of this space, potentially through Na^+/H^+ exchange. Low extracellular pH and the accumulation of protons in this space from the dissociation of CO_2 would produce an unfavorable ion gradient for this proton-equivalent ion exchange. As pH at the site of calcification decreases, CO_2 hydration and CO_3^{2-} formation would decrease, which could be reflected in decreases in calcification. Organisms that are able to compensate for this proton might not experience any effects on calcification and might be able to exploit the increased availability of bicarbonate for increased calcification in CO_2-acidified cellular spaces. We speculate that internal acidosis can be buffered by HCO_3^- through the dissolution of existing $CaCO_3$ skeletons or shells (99–101). This process may account for the dissolution of existing skeletons that has been documented in CO_2-acidified water (102–104).

Although disturbance to acid-base status is the current mechanism put forth by physiologists leading to CO_2 sensitivity of marine organisms (the mechanism is summarized in Reference 92), support for this mechanism is still incomplete. Because much of our understanding of the effects of hypercapnia has come from studies using extremely high levels of CO_2 more relevant to CO_2 sequestration scenarios (10,000 ppm CO_2), still unclear is whether elevated CO_2 levels more relevant to IPCC (Intergovernmental Panel on Climate Change) emission scenarios (550 ppm–1200 ppm CO_2) elicit acid-base disturbances. At present, few studies measure acid-base parameters in conjunction with other biological processes such as calcification or reproduction, and therefore whether these organisms experience internal acidosis is unknown. Future studies measuring intracellular as well as extracellular pH, pH_i, and pH_e are necessary to assess more accurately the capacity of organisms to maintain acid-base balance in the face of OA and to uncover the mechanisms underlying the sensitivity of higher-level processes such as development, growth, and reproduction.

Mechanistically, phenotypic plasticity during development may be a potential response to changing ocean chemistry (105), although some studies have noted the resilience of early life-history stages in response to stressors (106). A body of literature on the impacts of ocean acidification on embryos and larvae suggests that species and developmental stages respond differently, as has been noted for the complexity in calcification studies on phytoplankton (79). For example, in larvae of a brittlestar, Dupont et al. (107) found that a 0.2 decline in pH (pH 8.1 versus pH 7.9) resulted in skeletal abnormalities and high mortality after several days in culture; similar changes in skeleton morphometrics were also observed in a temperate sea urchin (108). In contrast, CO_2-acidified seawater at pHs as low as pH 7.6 had no effect on gastrulation in a temperate Australian sea urchin

IPCC: Intergovernmental Panel on Climate Change

(109). In a multispecies study, low-pH conditions were shown to deleteriously affect calcification of the larval skeleton in tropical and temperate sea urchin larvae, but not a cold-adapted Antarctic species (110). Mechanistically, transcriptomic analysis of gene expression in purple sea urchin larvae raised under CO_2-acidified conditions found an expression profile that suggested mild metabolic depression rather than the large defensome response that characteristically occurs with thermal stress (41).

The expanding literature on ocean acidification is documenting subtle effects when seawater is CO_2 acidified to pHs that are near IPCC-predicted scenarios. Future work in this area would benefit from two study approaches: (*a*) multistressor studies that highlight the interaction of OA with other climate-change factors such as elevated temperature and (*b*) measurement of physiological costs to other biological processes (e.g., metabolism or the stress response). Understanding the interaction of these mechanisms will be critical (94, 111). Notably, in a study on regeneration in a brittlestar, although calcification rates and metabolic rates increased in response to low pH, muscle wastage was noted as a deleterious cost of this apparent compensation to defend regeneration-associated calcification under OA conditions (112).

INTERACTING AND SYNERGISTIC STRESSORS

Global climate change presents the distinct possibility that organisms will experience multiple stressors simultaneously, a well-recognized scenario (e.g., 113–115). Historically, plants have lent themselves to deeper study of multiple stressors that naturally occur together, e.g., heat stress and drought. In *Arabidopsis*, for example, differential gene expression underlies a variable response to two stressors (116). From a mechanistic perspective, responses to multiple stressors are complex and often present an entirely new perspective on the ability of physiological plasticity to compensate for climate change drivers. Here, the trade-offs or costs elements, i.e., to what extent an effective response to one stressor limits the response to another (117), may have a major influence on the capacity of organisms to acclimatize to new environmental conditions. In some cases, the outcome is additive tolerance: Tolerance for one stress increases tolerance for an additional stress [e.g., desiccation and heat stress in *Drosophila* (118), additive thermal stresses in a tropical coral (119)]. In other systems, however, interactions among multiple stresses have negative consequences. Below, we highlight two significant potentially interacting stressors: temperature and ocean acidification and temperature and desiccation.

Temperature and Ocean Acidification

In the laboratory, crabs (*Cancer paguarus*) exposed to elevated (1%) CO_2 displayed a 5°C reduction in the upper thermal limits of aerobic scope (120). Similarly, low pH reduces the metabolic rate of pelagic squid, and elevated temperatures exacerbate this reduction (97). Additionally, for echinopluteus larvae of the red sea urchin, development at low pH resulted in a reduced ability to express genes involved in cellular defense in response to heat stress (111). This work suggests that a loss of thermal tolerance is reflected in changes of key transcripts for genes in the urchin defensome, a key mechanism of defense in early life-history stages (106). Similarly, elevated pCO_2 conditions that mimic ocean acidification increased sensitivity to temperature in coralline algae (121), an outcome also noted for corals (122). In another laboratory manipulation of stony corals, acidification and warming had a synergistic effect and reduced calcification and productivity, although coral species (members of *Acropora* and *Porites*) differed in their responses (123). Furthermore, during a 16-year study, synergistic stressors were linked to a decline in calcification in corals of the Great Barrier Reef (124). Overall, the results of these few studies underscore the importance of further exploration of interacting and synergistic stressors in a climate change context. Studies such as these, highlighting how compensation to one stressor affects sensitivity to another, will

greatly inform predicting the vulnerability of species in a multistressor environment.

Temperature and Desiccation

Desiccation stress is another result of co-occurring stressors—in this case, elevated temperature and low water availability and water stress. In general, physiological responses to desiccation involve the preservation of hydration and/or the tolerance of dehydration. Obviously, behavior can be a significant response to desiccation such that, for example, animals can decrease their exposure to desiccating conditions by choosing shade or foraging at night. Insects can exemplify the physiological mechanisms underlying an organism's response to desiccation. As many studies show, insects have a distinct critical temperature above which water loss increases rapidly, presumably due to the biochemical constituents of the insect cuticle. A lipid-melting model (125) relates the critical temperature to lipid phase state and cuticular permeability: The cuticular lipid composition affects permeability and hence desiccation resistance. A similar strategy is noted in birds, in which cutaneous water loss is thought to be primarily mediated through changes in the lipid composition of the stratum corneum (e.g., 126). Notably in insects, desiccation resistance has a high heritability in some *Drosophila* species (127). Invasive North American populations of *Drosophila subobscura* have rapidly evolved desiccation resistance within the past 30 years, with more arid populations having a higher desiccation tolerance (128). This might not be the case for all *Drosophila* species, as research has shown that *Drosophila birchii*, a rainforest species, was unable to evolve additional desiccation resistance (129). As desiccation-intolerant species already tend to have a more narrow distribution, these species may be more vulnerable to climate change.

SUMMARY REMARKS

This review has two purposes: (*a*) to highlight physiological mechanisms and their potential to serve as components of physiological plasticity in contemporary and future organisms in response to climate change drivers and (*b*) to underscore the important roles that ecological and comparative physiology have to play in predicting the response of organisms to global climate change. The conservation-oriented approach has been highlighted previously for reliance on such techniques as telemetry (130), but we propose that the more traditional "skin in" approach can link powerfully to the "skin out" approaches often used to examine community- and ecosystem-level impacts of climate change. The role of Arctic pteropods as important constituents of the diet of salmon exemplifies our proposition. Pteropods, calcifying pelagic gastropods, were estimated to be 40% of the stomach contents of some salmon species when salmon are transitioning between food sources (131). Ocean acidification is predicted to have a deleterious effect on calcification of pteropods (104), thereby threatening their availability to salmon in a critical feeding window. Pteropods may be unable to migrate to where aragonite saturation levels are more suitable for calcification if their destination is a lower latitude, which these cold-adapted invertebrates may not tolerate. Even if the salmon could comigrate with their food source, these fish would then encounter environments to which they are not adapted. The complex interplay of the tolerances of different life-history stages could result in deleterious interactions of stressors, making consequences of changes in migration patterns complex and unpredictable (132). Thus, understanding the mechanistic basis for the responses to changes in the physical environment may indeed inform how these changes will play out at the ecosystem and species interaction levels.

Research Choices and Priorities

We must apply our efforts and research dollars to best address physiological mechanisms and the balance of plasticity versus evolutionary rescue in a framework that has relevance to understanding the effects of GCC (2). One

LT_{50}: lethal temperature, 50%

approach is a "vulnerability matrix" that maps out research questions that highlight the role of acclimatization and acclimation in a species (57, 133), focusing on especially vulnerable species (51, 104, 134) or those playing key ecological roles (e.g., 80, 97, 104, 135–137).

The last IPCC report presented climate change scenarios as global averages (138). Populations and even individuals are unlikely to respond to this global scale of change, however. Regional scale processes are likely a better indicator of geographic range limits (62, 139). These regional changes differ from the global averages and highlight the importance of choosing species for study or conservation based on "regions" that are the most likely to undergo large changes or contain species close to their limits (1).

Ecoregional Hotspots for Further Study

Animals in very stable habitats (e.g., tropical and polar environments) have been suggested to be less tolerant of environmental change (52, 55, 134, 140). Even in temperate regions with greater selection for tolerance of environmental variability, intertidal species likely already approach their thermal tolerance limits (26, 141, 142). These species therefore seem particularly vulnerable to increases in ambient temperature as well as more frequent summer extreme temperature events. In porcelain crabs, the ABT for heart function as well as LT_{50} are close to the maximum habitat temperature for intertidal crabs, although 10°C below that for subtidal crabs (143). Similarly, intertidal snails (*Tegula*) have an ABT that is within 1°C of their highest measured field body temperature (141). Also, these species have a limited ability to increase ABT during warm acclimation. These data strongly suggest that the adaptation-acclimation potential of an organism is limited and that intertidal organisms may be close to exhausting this potential and therefore are already living very close to their thermal tolerance limits. Because failure of heart function is very close to upper thermal limits, for these species heart function is the weak link defining thermal tolerance and, as a result, may be a key determinant of the species' range. For animals already existing on the edges of their tolerance windows, a few degrees' change can be highly deleterious. Multidecadal increases in seawater temperature of 2°C correlated with major faunal shifts in intertidal and subtidal habitats (144). In addition, recent extreme temperature events exceed the physiological capacity of intertidal organisms. The years 1998 and 2005 had some of the highest temperatures on record (138), and these extreme temperature events have been linked to mass mortality of intertidal invertebrate communities (e.g., 145, 146) as well as of coral reef communities (53).

Finally, we urge studies that identify species, life-history stages, and ecological interactions that are most vulnerable to climate change. Physiological information about keystone species, key members of food webs, and critical organisms in an ecosystem should elucidate how community-level processes will change. Given the implications of a changing climate and a changing ocean for society, such work should contribute to decision making (147) as governments and agencies in all nations respond (138).

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