Hypoxia and High Temperature as Interacting Stressors: Will Plasticity Promote Resilience of Fishes in a Changing World?

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Abstract

Determining the resilience of a species or population to climate change stressors is an important but difficult task because resilience can be affected both by genetically based variation and by various types of phenotypic plasticity. In addition, most of what is known about organismal responses is for single stressors in isolation, but environmental change involves multiple environmental factors acting in combination. Here, our goal is to summarize what is known about phenotypic plasticity in fishes in response to high temperature and low oxygen (hypoxia) in combination across multiple timescales, to ask how much resilience plasticity may provide in the face of climate change. There are relatively few studies investigating plasticity in response to these environmental stressors in combination; but the available data suggest that although fish have some capacity to adjust their phenotype and compensate for the negative effects of acute exposure to high temperature and hypoxia through acclimation or developmental plasticity, compensation is generally only partial. There is very little known about intergenerational and transgenerational effects, although studies on each stressor in isolation suggest that both positive and negative impacts may occur. Overall, the capacity for phenotypic plasticity in response to these two stressors is highly variable among species and extremely dependent on the specific context of the experiment, including the extent and timing of stressor exposure. This variability in the nature and extent of plasticity suggests that existing phenotypic plasticity is unlikely to adequately buffer fishes against the combined stressors of high temperature and hypoxia as our climate warms.

Introduction

Water temperature and oxygenation are critical factors that affect the performance of fishes, and both are being altered by human activities (Cahill *et al.*, 2013; Barros *et al.*, 2014; Gattuso *et al.*, 2015; Luypaert *et al.*, 2020; Albert *et al.*, 2021). As such, it is not surprising that these two factors have been highlighted in a range of influential theories that attempt to use physiological parameters to understand the principles underlying the distribution and abundance of aquatic animals and how they may be affected by climate change. These include the theory of oxygen- and capacity-limited thermal tolerance (OCLTT) (Pörtner, 2002; Pörtner and Lannig, 2009; Pörtner *et al.*, 2017), the oxygen- and temperature-limited metabolic niche framework (Ern, 2019), the theory of gill oxygen limitation (GOLT) (Pauly and Cheung, 2018; Pauly, 2021), and the concept of the metabolic index (Deutsch *et al.*, 2015, 2020). While many of these theories remain controversial (Lefevre *et al.*, 2017; Jutfelt *et al.*, 2018), all emphasize the importance of interactions between oxygen and temperature. As such, there is an urgent need to understand the interactive impacts of warming waters combined with decreases in oxygen to predict how fish populations will cope with anthropogenic climate change.

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Abbreviations: CTMax, critical thermal maximum; F1, embryo; F2, embryonic germ cell; LOE, loss of equilibrium.

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Interacting Effects of Hypoxia and High Temperature

Temperature plays a critical role in determining water oxygenation through multiple mechanisms (Fig. 1). Increased temperature directly lowers water oxygenation by decreasing gas solubility, although this decrease may be largely offset by increases in the rate of diffusion as temperature rises, which increases oxygen delivery to the organism (Verberk *et al.*, 2011). Climate change also indirectly affects water oxygenation by changing ocean circulation patterns and mixing, thus reducing the ventilation of the ocean (Keeling and Garcia, 2002; Matear and Hirst, 2003; Keeling *et al.*, 2010; Somero *et al.*, 2015). However, the largest effects of high temperature on aquatic oxygen levels occur because high temperatures increase the metabolic demand of a variety of microorganisms, such as bacteria and algae. This effect is particularly important in areas where human activities increase nutrient input into aquatic systems through runoff of agricultural fertilizer and wastewater, which reduces the nutritional constraint on the microbial growth (Smith and Schindler, 2009). These rapidly growing microorganisms can drastically decrease water oxygen levels and cause hypoxic dead zones in which fish cannot survive (Diaz and Rosenberg, 2008; Altieri and Gedan, 2015). This effect is exacerbated at night when photosynthetic organisms are respiring but not photosynthesizing (Diaz and Rosenberg, 2008; Diaz and Breitburg, 2009; Altieri and Gedan, 2015; Somero *et al.*, 2015; Jenny *et al.*, 2016). Because of these multiple interacting effects, aquatic hypoxia is likely to occur more frequently for longer periods of time, to more extreme levels, and across a wider range of habitats as our climate warms (Matear and Hirst, 2003; Diaz and Rosenberg, 2008; Diaz and Breitburg, 2009; Altieri and Gedan, 2015; Breitburg *et al.*, 2018). For example, the mass mortality events known as summerkill that occur in lakes in the north-temperate zone, due to relatively transient episodes of high temperature and low oxygen, are predicted to increase more than fourfold by 2100 in northern latitudes (Till *et al.*, 2019).

In addition to these environmental interactions, high temperature and hypoxia also have interacting effects on the fish themselves. These interactions are thought to be mediated through the joint impacts of high temperature and hypoxia on metabolism (Fig. 1; Fry and Hart, 1948; Precht, 1958; Prosser, 1969; Fry, 1971; Hazel and Prosser, 1974; Hochachka and Somero, 2001). Rising temperatures

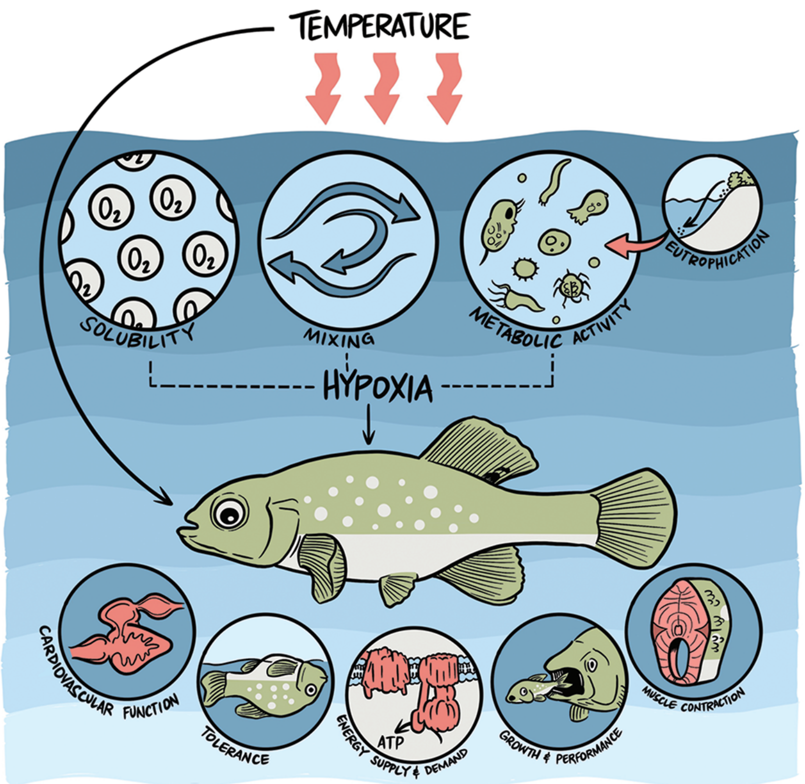

Figure 1. Interactive effects of oxygen and temperature in aquatic environments. High temperature increases the likelihood of aquatic hypoxia by decreasing gas solubility, altering mixing, and increasing the metabolic activity of microorganisms. Particularly in areas affected by eutrophication, this can cause large declines in water oxygenation, resulting in hypoxia or anoxia. High temperature and hypoxia also have interacting effects on fish through their joint effects on energy supply and demand, because increasing temperature increases demand while hypoxia reduces energy supply. These effects at the biochemical level cascade up to affect processes at the physiological level, such as cardiovascular and muscle function, which in turn affect whole-organism growth and performance and tolerance. ATP, adenosine triphosphate.

increase the rates of chemical and biochemical reactions (Schulte, 2015; Somero *et al.*, 2017); and these thermodynamic effects result in increases in metabolic demand, which must be met with increases in metabolic energy supply for an organism to maintain energy balance. For many animals, this energy supply will be provided through aerobic metabolism, and this supply can become limited when environmental oxygen declines (McBryan *et al.*, 2013; Schulte, 2015). These effects at the biochemical level cascade up to affect processes across levels of biological organization, with profound effects on complex physiological processes, such as cardiovascular function, muscle contraction, metabolism, energy budgets, and growth, which impact organismal growth and performance as well as thermal and hypoxia tolerance (Schulte, 2015; Somero *et al.*, 2017; Little *et al.*, 2020). The combination of high temperature and hypoxia in the environment is particularly devastating because high temperatures increase metabolic demand and simultaneously increase the prevalence and severity of environmental hypoxia, which limits the ability to supply this demand aerobically (Pörtner, 2001; McBryan *et al.*, 2013; Deutsch *et al.*, 2015; Schulte, 2015).

Timescales of Environmental Change

Both temperature and oxygen levels change in the environment across multiple timescales. Anthropogenic climate change is associated with a relatively gradual warming in temperature at a global scale, but it is also causing an increased frequency of heatwaves and extreme hypoxic events at local scales (Harvey *et al.*, 2022). These two processes affect organisms across different timescales, and both are likely to be important in determining how well organisms will be able to cope with our changing world. The importance of mean temperatures for shaping the distribution and abundance of fishes is evident in the close relationship between the temperatures that maximize growth and reproductive performance in the wild and the mean temperature of warm range boundaries in fish (Payne *et al.*, 2016). Similarly, the close correspondence of the metabolic index (a measure of temperature-dependent hypoxia tolerance) with biogeographic range boundaries supports an important role for mean temperature and oxygenation in shaping species distributions (Deutsch *et al.*, 2015, 2020). However, there is substantial evidence that changes in the extent and frequency of extreme temperature events, such as heatwaves, are a major driver of biodiversity loss in the Anthropocene (Sandblom *et al.*, 2014; Vasseur *et al.*, 2014; Buckley and Huey, 2016; Frölicher *et al.*, 2018; Román-Palacios and Wiens, 2020; Cheung *et al.*, 2021; Harvey *et al.*, 2022). The importance of extreme temperatures in shaping species' distribution and abundance is clear in the close correspondence between laboratory measures of acute thermal tolerance, such as the critical thermal maximum (CTMax) and latitudinal patterns in thermal extremes (Sunday *et al.*, 2019). Similarly, transient episodes of extreme hypoxia can have devastating effects on fish populations and likely shape fish species distribution and abundance. Indeed, a recent meta-analysis suggests that hypoxic events may be a more important driver of biodiversity change in the ocean than either temperature or ocean acidification (Sampaio *et al.*, 2021). Thus, both long-term gradual changes in temperature and oxygenation and the increased frequency of extreme events pose challenges for aquatic organisms.

Physiological responses to, and tolerance of, short-term events, such as heatwaves and acute hypoxia, are likely to be quite different from responses to more gradual changes; thus, timescales of exposure to climate change-relevant stressors become critically important when attempting to predict the likely resilience or sensitivity of fishes to climate change. When acutely exposed to high temperature or hypoxia (such as during a heatwave or a hypoxic summerkill), organisms must rely on their existing tolerance mechanisms. In addition, tolerance limits can be modified by prior environmental experience through various forms of phenotypic plasticity acting at different timescales. Thus, organismal responses across longer timescales interact with their tolerance of acute events.

Types of Phenotypic Plasticity

Developing an understanding of the causes and consequences of phenotypic responses to hypoxia and high temperature is complicated by the fact that the literature on phenotypic plasticity is rife with alternative terms for similar processes or the same term being used in different ways (Piersma and Drent, 2003; Bowler, 2005; Ghalambor *et al.*, 2015). In particular, physiologists and evolutionary biologists often approach this topic from very different perspectives and use different terminology (Huey and Berrigan, 1996); thus, it is important that we define the terms as we are using them here. We consider "phenotypic plasticity" to be a general term that describes the ability of an organism to change its phenotype in response to a change in the environment. In its broadest sense, this could refer to everything from instantaneous responses such as changes in heart rate to changes that persist over many generations. Whether very rapid and reversible phenotypic responses such as adjustments in heart rate and ventilation should be considered to represent phenotypic plasticity is a matter of debate (Woods and Harrison, 2002). Here we prefer to refer to these very rapid, and generally passive, effects occurring on a timescale of seconds to minutes as acute responses, although they have also been described as representing passive plasticity. We prefer to reserve the term "phenotypic plasticity" to refer to processes that involve active changes in biochemical properties that are regulated by the organism, such as changes in gene expression, membrane composition, or enzyme function. Here we discuss three main types of plasticity acting across different timescales (Fig. 2): acclimation, developmental plasticity, and intergenerational or transgenerational plasticity.

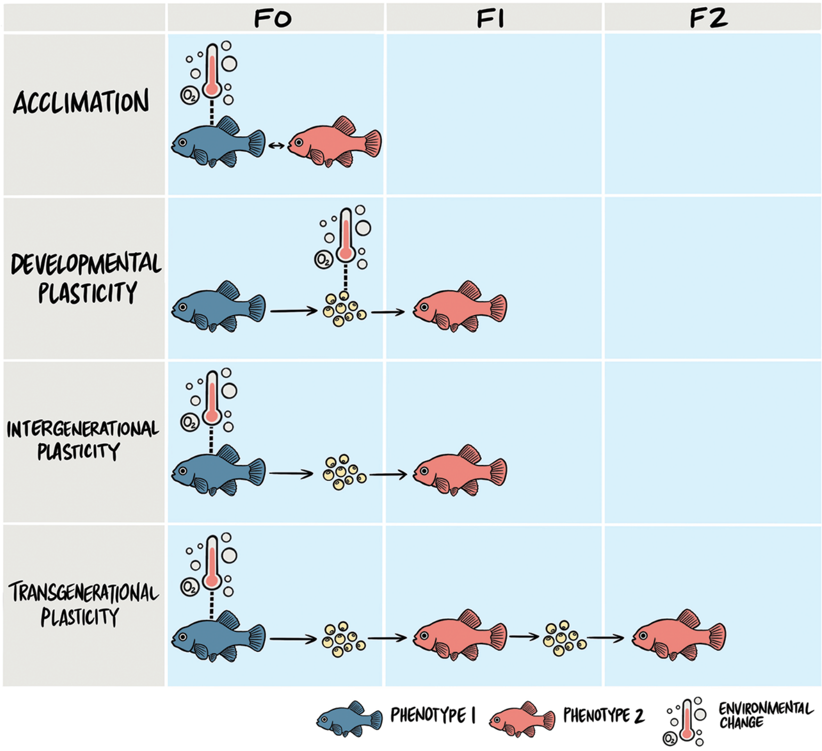

Figure 2. Types of plasticity across timescales. F0, parental generation; F1, embryo; F2, embryonic germ cell.

Acclimation is a type of plasticity that acts across relatively short time periods (hours, days, weeks, or months) and is generally considered to be reversible, such that the phenotype will revert to its original state if the environment returns to its original condition. Acclimation is thus often classified as an example of reversible plasticity, and the term "phenotypic flexibility" has also been proposed to distinguish this type of reversible phenotypic change from processes that result in more permanent changes in phenotype (Piersma and Drent, 2003; Woods, 2014). For simplicity, we also include phenomena such as heat hardening and the heat shock response with acclimation responses (Piersma and Drent, 2003; Bowler, 2005), because these processes are distinguished from the more classical view of acclimation and acclimatization largely based on the timescale and intensity of the exposure rather than on any fundamental difference in the process of the response (Bowler, 2005; Loeschcke and Sørensen, 2005).

Developmental plasticity occurs when the environment experienced during a particular critical window during development induces long-lasting, and often irreversible, changes in the phenotype (Burggren and Mueller, 2015). However, it is important to note that developmentally plastic traits exhibit a range of reversibility, depending on the type of exposure and the phenotype being examined (Burggren, 2020). There are also important interactions between developmental plasticity and acclimation (Beaman *et al.*, 2016). For example, developmental exposures to environmental conditions such as altered temperatures can affect the capacity for acclimation at the adult stage (Scott and Johnston, 2012; Seebacher *et al.*, 2014).

Intergenerational and transgenerational plasticity occur when the environment experienced by one generation affects the phenotype of individuals in subsequent generations (Mousseau and Fox, 1998; Jablonka and Raz, 2009; Ho and Burggren, 2012; Salinas and Munch, 2012; Donelson *et al.*, 2018; Chang *et al.*, 2021). We consider the term "intergenerational plasticity" to refer to changes acting across a single generation (from parent to offspring) that could be due to a wide range of maternal or paternal effects, including mechanisms such as transfer of lipids or hormones *via* the egg but that wash out in subsequent generations. We prefer to reserve the term transgenerational plasticity (which is also referred to as multi-generational plasticity) for phenomena that can be transmitted across multiple generations, usually meditated by more stable epigenetic mechanisms, such as changes in DNA methylation. However, we acknowledge that this distinction is not always made, and it can be difficult to draw the line between these phenomena because there are many potential interactions between them.

Is Plasticity Beneficial?

Plasticity of all types can result in significant phenotypic variation within and between populations, across life stages, and across generations and thus has the potential to play an important role in shaping species' responses to climate change (Vagner *et al.*, 2019). However, the extent to which plasticity of any type is adaptive (or even beneficial) has been the subject of extensive debate (Leroi *et al.*, 1994; Wilson and Franklin, 2002; Woods and Harrison, 2002; Ghalambor *et al.*, 2007; Seebacher *et al.*, 2015). In general, the range of environments over which plasticity can be induced and the range over which the induced changes may be beneficial varies between organisms and between traits. Thus, the extent of beneficial plasticity of any given individual or species, if any, has clear limits (Auld *et al.*, 2010; Norin and Metcalfe, 2019). Beyond some environmental threshold, a compensatory strategy may no longer be possible, and the organism may shift toward a passive endure-and-survive strategy. Ultimately, exposure to environments beyond those limits is likely to induce phenotypic changes that reflect harm or damage to the organism that could be beyond its capacity to repair.

The types of plastic responses that occur in response to environmental change have largely been considered in the context of acclimation. More than 65 years ago, Precht classified thermal acclimation responses into 5 groups (Fig. 3A), although these responses are relevant to plasticity acting at any timescale. This classification is based on the change in phenotype after acclimation relative to the effects of acute exposure to the stressor (Precht, 1958; Cossins and Bowler, 1987; Huey and Berrigan, 1996). For example, acute exposure to high temperature is expected to cause an increase in the rate of many biological rate processes (*e.g.*, metabolic rate). After acclimation, if the phenotype returned to its control level, Precht (1958) considered this to be "complete compensation," whereas "over-compensation" represented an overshoot in acclimation such that the rate after acclimation was lower than the control rate. Alternatively, in "inverse compensation" the rate following acclimation was greater than the rate with acute exposure. Note that Precht framed these responses in a context that implies that the ideal result of acclimation would be complete return to the phenotype observed under control conditions. However, as pointed out by multiple authors (Huey and Berrigan, 1996; Einum *et al.*, 2019), for many traits (including metabolic rate) it is extremely difficult to establish, *a priori*, whether complete compensation is likely to be beneficial, because the optimal phenotype under the new environmental conditions is not always known. Thus, any one of these types of responses might represent beneficial acclimation or, alternatively, could be a pathological response. However, defining compensation for tolerance traits is relatively straightforward, because improved tolerance is unequivocally beneficial. Thus, complete compensation or overcompensation of tolerance would represent beneficial acclimation to high temperature, whereas inverse compensation would be consistent with a stressful or pathological effect.

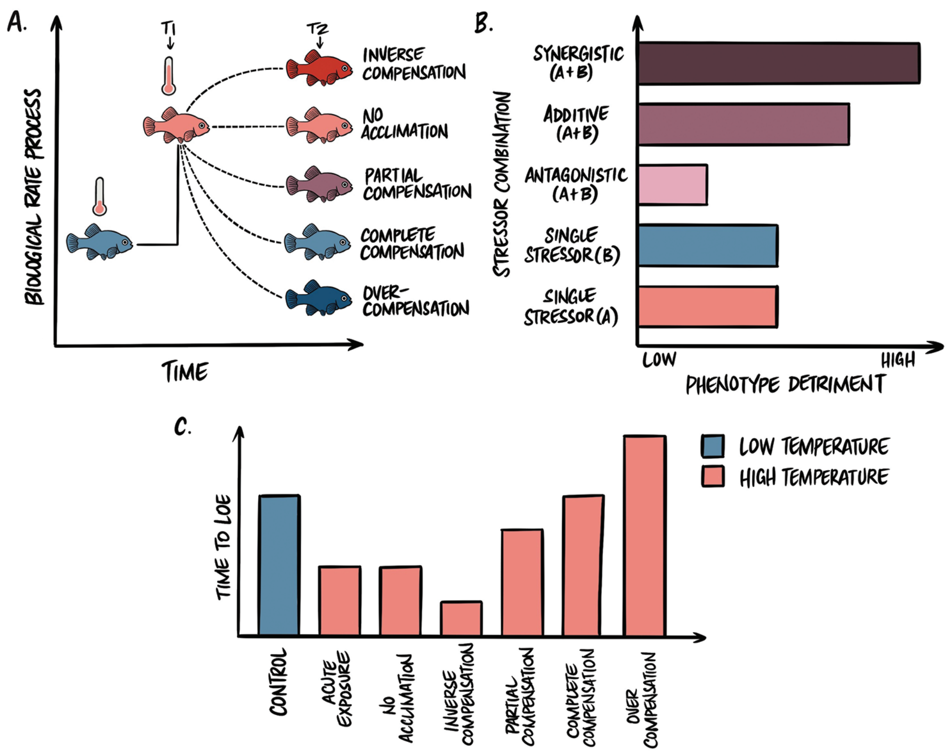

Figure 3. Effects of interacting stressors and processes of compensation through plasticity. (A) Types of compensatory responses. Acute transfer to an elevated temperature (at timepoint 1, T1) has immediate and direct thermodynamic effects on biological rate processes. Over time (T2), phenotypic plasticity may allow one of five types of responses. (B) Possible effects of interacting stressors on organismal phenotypes. (C) An example of potential types of acclimation responses across interacting stressors for the effects of high temperature acclimation on hypoxia tolerance (measured as time to loss of equilibrium [LOE]).

 Biol. Bull. 2022, 243: 149–170

The Challenge of Interacting Stressors

The majority of studies of resilience to environmental stressors have examined single stressors in isolation, whereas studies of the effects of interacting stressors are less common (Todgham and Stillman, 2013; Przeslawski *et al.*, 2015; Gunderson *et al.*, 2016; Jackson *et al.*, 2016). In principle, when an organism is exposed to more than one stressor in combination, the resulting effect on performance may be additive, antagonistic, or synergistic (Folt *et al.*, 1999; Crain *et al.*, 2008; Todgham and Stillman, 2013; Gunderson *et al.*, 2016; Fig. 3B).

For acute exposure to both high temperature and hypoxia in combination, the available evidence suggests that these stressors act synergistically on fish (Fig. 3B). Such exposure to high temperature and low oxygen together causes greater decrements in performance than would be expected based on the response to either stressor alone across a wide range of traits (Claireaux *et al.*, 2000; Shimps *et al.*, 2005; Schurmann and Steffensen, 2006; Nilsson *et al.*, 2010; Healy and Schulte, 2012; McBryan *et al.*, 2016; Townhill *et al.*, 2017; Jung *et al.*, 2020; Nudds *et al.*, 2020; Somo *et al.*, 2020). For example, acute transfer to high temperature markedly decreases the ability to tolerate acute exposure to hypoxia in most fish species (Fig. 3C).

Under control conditions at a moderate temperature, a fish will be able to maintain the appropriate orientation in the water column when exposed to severe hypoxia for a certain period (time to loss of equilibrium [LOE]), through a combination of increased oxygen extraction from the water and recruiting anaerobic pathways to help maintain adenosine triphosphate (ATP) supply. This time gets shorter when a fish is also acutely exposed to higher temperatures, because the higher temperatures cause an increase in metabolic demand, which causes a more extreme imbalance between energy demand and supply, shortening the time to LOE.

However, the exact extent of these interactions depends on the species and the particular levels of temperature and hypoxia that are tested (McBryan *et al.*, 2016; Jung *et al.*, 2020; Jensen and Benfey, 2022). The variability between species in the interactive effects of high temperature and hypoxia is clearly illustrated in a study by Jung *et al.* (2020), who examined effects on hypoxia tolerance at several different acute thermal exposures across multiple species. They found that some species exhibited negative effects on hypoxia tolerance with quite small increases in temperature (from 30 °C to 33 °C) and that other species did not show effects on hypoxia tolerance until temperatures increased from 30 °C to 37 °C (Jung *et al.*, 2020). Following these acute effects, over time, depending on the species and the specific conditions, fish may induce plastic responses that alter their ability to tolerate hypoxia at high temperatures and that may change the time to LOE and result in one of the possible forms of compensation (Fig. 3C).

Most studies that have examined the nature and extent of various types of plasticity in response to exposure to high temperature or hypoxia have been conducted by examining the effects of each stressor in isolation. However, to understand and predict effects of human activities on aquatic biodiversity and to estimate the relative resilience of species as aquatic environments become warmer and more hypoxic, we must be able to untangle the independent and interactive effects of combined stressors and the extent of beneficial or harmful plastic responses to these combined stressors (Collins *et al.*, 2021). Currently, the poor understanding of how fish will respond to changes in temperature and oxygenation makes it difficult to develop predictive models of how fish distribution and abundance will shift as our climate changes (Cahill *et al.*, 2013; Todgham and Stillman, 2013). Therefore, our goal in the remainder of this review is to survey the current state of knowledge of the extent of plasticity in response to combined exposure to hypoxia and elevated temperature on fish across different timescales, with the goal of asking whether beneficial phenotypic plasticity has the potential to help fish cope with our rapidly changing environment.

Evidence for Beneficial Acclimation

Detecting acclimation in response to hypoxia or high temperature can be challenging because it requires information about the acute effects of the stressor. To illustrate this issue, consider the data presented in Figure 4A. In this experiment, Atlantic killifish (*Fundulus heteroclitus* (Linnaeus, 1776)) were acclimated to either 15 °C or 23 °C for several weeks, and then hypoxia tolerance was tested by measuring time to LOE at their respective acclimation temperatures (McBryan *et al.*, 2016). Time to LOE decreased by 36% between fish acclimated at 15 °C and 23 °C, suggesting that high temperatures have a negative effect on hypoxia tolerance. In the context of climate change, these data suggest that fish will have more difficulty dealing with hypoxia as our climate warms. However, these data cannot be used to evaluate the extent, if any, of the acclimation response because the acute effects of exposure to high temperature are not accounted for. To assess the extent of the acclimation response, the data shown in Figure 4B are also needed. Here, hypoxia tolerance (time to LOE in severe hypoxia) was tested in fish acclimated to 15 °C after acute transfer to either 15 °C or 23 °C (McBryan *et al.*, 2016). Acute transfer to 23 °C caused time to LOE to decline by 94% relative to fish tested at 15 °C. A comparison of the hypoxia tolerance of 15 °C acclimated fish acutely transferred to 23 °C (Fig. 4B) to the hypoxia tolerance of fish that have had time to acclimate (Fig. 4A) shows that there is considerable beneficial plasticity of hypoxia tolerance in response to thermal acclimation. However, fish acclimated and tested at 23 °C are still less tolerant of hypoxia than are fish acclimated and tested at 15 °C, indicating only partial compensation.

Only a subset of studies of acclimation to increased temperature and/or hypoxia have designs that are suitable to assess the extent of the acclimation response. For example, in

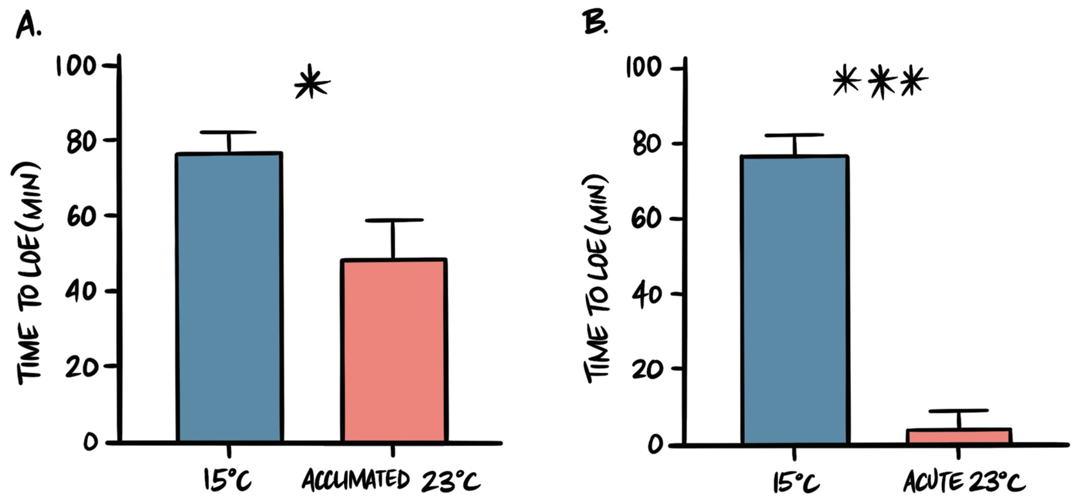

Figure 4. The importance of accounting for acute effects when estimating the extent of plasticity. (A) Hypoxia tolerance measured as time to loss of equilibrium (LOE) in fish acclimated to and tested at 15 °C or acclimated to and tested at 23 °C. (B) Hypoxia tolerance measured as time to LOE in fish acclimated to 15 °C and tested at either 15 °C or 23 °C. Data from (McBryan *et al.*, 2016). *$P < 0.05$; ***$P < 0.001$.

a meta-analysis of studies examining plasticity in metabolic rate with temperature acclimation in ectotherms, Havird *et al.* (2020) showed that only 26% of studies across all ectotherms (or 30% in fish) contained information on the extent of both the acute effect of temperature and the phenotype after acclimation. Their analysis of the studies that control for these acute effects demonstrated that compensatory acclimation responses were common in fish and were particularly pronounced in marine species. However, the majority of studies showed only partial compensation of metabolic rate, and complete compensation was rare (Havird *et al.*, 2020). There were also many cases in which no compensation was detected or where acclimation exacerbated the effect of acute exposure, resulting in inverse compensation. Similarly, variable results across taxa were detected using a somewhat different approach in a meta-analysis that calculated the temperature coefficient (Q_{10}) of metabolic rate and several related traits at lower levels of biological organization in both acutely exposed and thermally acclimated ectotherms (Seebacher *et al.*, 2015). The results of these studies emphasize the importance of assessing both acute effects and the phenotype following acclimation if the goal is to assess the extent of plasticity. These analyses also clearly demonstrate that acclimation can only partially offset the acute effects of high temperature exposure in most species. However, it is also important to remember that the optimal phenotype under the new conditions is not always known, and complete compensation of the phenotype with acclimation may not always be the most beneficial response; interpretations of the benefits of patterns of partial compensation need to take this possibility into account.

We are not aware of any currently published meta-analyses examining the extent of the acclimation response to hypoxia in aquatic ectotherms that consider the acute effects of exposure. However, several meta-analyses have documented adverse effects of even modest hypoxia across a range of aquatic taxa, either acutely or in acclimated animals (Hrycik *et al.*, 2017; Galic *et al.*, 2019). Conversely, many studies suggest that fish have substantial capacity to compensate for the acute effects of hypoxia after acclimation (Lomholt and Johansen, 1979; Rees *et al.*, 2001; Routley *et al.*, 2002; Richards, 2009; Fu *et al.*, 2011; Yang *et al.*, 2013; Dan *et al.*, 2014; Collins *et al.*, 2016; Pan *et al.*, 2017; Gilmore *et al.*, 2019), suggesting that beneficial acclimation is possible in at least some taxa.

Studies of the interactive effects of high temperature and hypoxia on fish are relatively rare, and those that also account or control for acute effects that can be used to estimate the extent of acclimation responses are even scarcer. These studies have a variety of designs, which fall into three main categories: (1) studies of the effects of prior (usually brief) exposure to one stressor on the subsequent response to another stressor, (2) studies of the effects of acclimation to one stressor on the response to another stressor, and (3) studies of the effects of acclimation to both stressors simultaneously. The first two study designs allow the detection of a phenomenon known as cross-tolerance, in which the mechanisms that are induced to protect against one stressor also confer protection against a second stressor (Sinclair *et al.*, 2013), whereas the third study design allows various types of interactions to be detected. Below we discuss the evidence for beneficial acclimation that has been obtained from each of these kinds of studies.

Effects of brief prior exposure to one stressor

The only experiments using this type of experimental design to detect cross-tolerance between high temperature and hypoxia exposure in fish have investigated the effects of a brief period of high temperature exposure on subsequent hypoxia tolerance; to our knowledge none have

 Biol. Bull. 2022, 243: 149–170

investigated the effects of brief periods of hypoxic exposure on thermal tolerance or any other temperature-related trait. Because these studies involve designs that expose fish to a brief episode of high temperature and then return them to cooler temperatures prior to assessing hypoxia tolerance, they are well suited for detecting the extent of cross-tolerance and beneficial acclimation. The subsequent measurement of hypoxia tolerance is thus not confounded by the acute effects of high temperature.

This experimental design is particularly relevant for intertidal fish that are likely to experience high temperatures at low tide during the day, when tidepools heat up, and hypoxia at night, when water temperatures are cooler and algae in intertidal pools are not photosynthesizing but are continuing to respire and reduce water oxygenation. There are two studies using this design in intertidal fishes (Todgham *et al.*, 2005; McArley *et al.*, 2020). Of these studies, one on tidepool sculpins (*Oligocottus maculosus* Girard, 1856), detected beneficial cross-tolerance as an increase in survival in extreme hypoxia (Todgham *et al.*, 2005); but the other, in New Zealand intertidal triplefin (*Bellapiscis medius* (Günther, 1861)), did not (McArley *et al.*, 2020). It is impossible to know whether the different patterns across studies in ecologically similar but phylogenetically distant fishes are due to differences in the severity of the initial heat shock, the amount of recovery time following the heat shock, the differences in the metrics of hypoxia tolerance assessed, or the intrinsic differences between the species. Heat-shock proteins have been hypothesized to be involved in the rapid cross-tolerance induced by brief exposure to high temperatures, but the link between these processes at the cellular level and whole-organism tolerance is not particularly strong (Todgham *et al.*, 2005). Therefore, it is important to be cautious when attempting to draw general conclusions about the ecological importance of cross-tolerance and its potential role in providing resilience in the face of climate change.

Effects of thermal acclimation on hypoxia tolerance

Many studies have examined the effects of thermal acclimation on hypoxia tolerance, but these studies measured hypoxia tolerance at the respective acclimation temperature (Barnes *et al.*, 2011; Remen *et al.*, 2013; He *et al.*, 2015; McDonnell and Chapman, 2015; Shi *et al.*, 2018; Jung *et al.*, 2019; Opinion *et al.*, 2021), which does not allow the extent of plasticity to be accurately assessed. Negative effects of thermal acclimation on hypoxia tolerance have been detected in many of these studies (Barnes *et al.*, 2011; Remen *et al.*, 2013; He *et al.*, 2015; McDonnell and Chapman, 2015; Shi *et al.*, 2018), but neutral or positive effects of thermal acclimation have been detected in others (He *et al.*, 2015; Opinion *et al.*, 2021). These studies reveal that climate-associated warming is unlikely to fully protect fish against exposure to hypoxia. However, because the acute effects of high temperature on hypoxia tolerance were not measured in these studies, they do not provide information about the extent of beneficial acclimation in these traits.

Only a few studies have adequately accounted for the acute effects of high temperature on hypoxia tolerance or performance, allowing the extent of beneficial plasticity for cross-tolerance to be detected. Beneficial cross-tolerance was detected in two species from northern temperate habitats, Atlantic killifish and brook char (*Salvelinus fontinalis* (Mitchill, 1814)), with warm acclimation acting to partially offset the negative effects of acute high temperature exposure on hypoxia tolerance in both species (McBryan *et al.*, 2016; Jensen and Benfey, 2022). There is relatively little known about the mechanisms that might underlie cross-tolerance of hypoxia tolerance following warm acclimation in temperate-zone fishes. In Atlantic killifish, warm acclimation is associated with an increase in lamellar surface area in the gill, increasing the surface area available for diffusion of oxygen, which might account for the observed cross-tolerance in this species (McBryan *et al.*, 2016).

It is important to appreciate the extremely narrow thermal window that results in beneficial acclimation and cross-tolerance between thermal acclimation and hypoxia tolerance. For example, in brook char (Jensen and Benfey, 2022), there was no effect of acute thermal exposure on hypoxia tolerance in fish acclimated to 18 °C when tested at temperatures at or below 24 °C and, thus, no evidence of (or need for) compensatory acclimation. In fish tested at 26 °C the negative effects of acute temperature on hypoxia tolerance were modest, and there was a small offset of these effects by warm acclimation. In fish tested at 28 °C, there were significant negative effects of acute exposure to high temperature on hypoxia tolerance, and there was substantial (but not complete) compensation of hypoxia tolerance after warm acclimation. By contrast, in fish tested at 30 °C, the negative acute effects of high temperature exposure on hypoxia tolerance were extreme, and warm acclimation was able to offset only a tiny fraction of this loss. Thus, it was possible to observe cross-tolerance only within a narrow window of test temperatures (26 °C to 28 °C) (Jensen and Benfey, 2022).

Unlike these studies with fish from temperate habitats in the northern hemisphere, studies in tropical fish have not detected any cross-tolerance between warm acclimation and hypoxia tolerance (Nilsson *et al.*, 2010). Similarly, there was no evidence of compensation of hypoxia tolerance by warm acclimation in multiple Amazonian species; instead, fish either exhibited no compensation or negative effects of warm acclimation on hypoxia tolerance, depending on the species (Jung *et al.*, 2020). At present, it is not possible to determine whether the difference in cross-tolerance between the north-temperate and tropical fishes is the result differences in the phenotypes assessed (*e.g.*, survival, time to LOE, O_2 at LOE), differences in the nature of the thermal or hypoxia exposure, or differences in the species used. Tropical fish tend to show less thermal plasticity than do temperate fish (McKenzie *et al.*, 2020; Nati *et al.*, 2021), and this might play a role in the observed differences between studies. However, the data from brook char demonstrate the extremely narrow range over which beneficial cross-tolerance is observed, even in temperate fishes with extensive capacity for thermal acclimation, which may account for some of the differences between studies.

Overall, although the paucity of available data limits our ability to make general conclusions, it is clear that cross-tolerance between thermal acclimation and hypoxia tolerance or performance in hypoxia is likely to occur only under a relatively narrow set of conditions and in a subset of species. At most, compensation through acclimation is only partial; thus, fish still do worse in the combination of high temperature and hypoxia than in hypoxia at lower temperatures, even after acclimation. Thus, warm acclimation has the potential to mitigate some of the acute effects of high temperature exposure on hypoxia tolerance, but it is clear that the capacity for acclimation is limited and the combination of high temperature and hypoxia as our climate warms is likely to be challenging for fish.

Effects of hypoxic acclimation on thermal tolerance

Far less is known about the effects of long-term hypoxic acclimation on thermal tolerance. In sablefish (*Anoplopoma fimbria* (Pallas, 1814)) acute exposure to hypoxia impaired CTMax and the cardiac and metabolic responses to warming, and hypoxic acclimation of four to six months did not improve performance in any of the metrics when measured in common hypoxic conditions (Leeuwis *et al.*, 2021). However, steelhead trout (*Oncorhynchus mykiss* (Walbaum, 1792)) acclimated to chronic hypoxia had the same CTMax and aerobic scope as control fish when tested under common normoxic conditions but exhibited a decrease in cardiac output and stroke volume, whereas oxygen utilization at the tissue level was improved after hypoxia acclimation (Motyka *et al.*, 2017). These data suggest that there are limited long-lasting negative effects of hypoxia acclimation in this species when the hypoxic exposure is removed. In channel catfish (*Ictalurus punctatus* (Rafinesque, 1818)), hypoxic acclimation resulted in a small but significant increase in CTMax tested under common conditions in normoxia (Burleson and Silva, 2011). In general, acute exposure to hypoxia has been shown to reduce CTMax in fish (Rutledge and Beitinger, 1989; Healy and Schulte, 2012; Ellis *et al.*, 2013; Leeuwis *et al.*, 2021), which suggests that channel catfish might exhibit some cross-tolerance in response to hypoxic acclimation. However, without acute exposure data from the same species, this conclusion remains tentative because it has not been tested directly. The differences in the response to hypoxic acclimation across species may be due to intrinsic differences between the species but could also be the result of differences in the nature and extent of the hypoxic acclimation across studies. At present, there are too few studies to draw strong conclusions, and additional studies in this area are urgently needed (Spicer *et al.*, 2019; Collins *et al.*, 2021; Rodgers and Gomez Isaza, 2021).

Effects of acclimation to combined stressors

Studies of acclimation in response to combined exposures to high temperature and hypoxia are much rarer than single-stressor studies (Collins *et al.*, 2021; Rodgers and Gomez Isaza, 2021). However, it is clear that acclimation to these combined stressors can be quite challenging for fish, and multiple studies suggest negative effects of combined exposure to these stressors across species and life stages (Stierhoff *et al.*, 2006; Del Rio *et al.*, 2019; Targett *et al.*, 2019; Sun *et al.*, 2020); there is some evidence of beneficial acclimation to combined exposures as well (Collins *et al.*, 2021; Rodgers and Gomez Isaza, 2021).

There are several studies that have used fully factorial designs with combinations of warm temperature and hypoxia. In both Arctic char (*Salvelinus alpinus* (Linnaeus, 1758)) and a landlocked form of Atlantic salmon (*Salmo salar* Linnaeus, 1758), warm acclimation improved hypoxia tolerance, but acclimation to nighttime hypoxia reduced CTMax (Anttila *et al.*, 2015). In Atlantic salmon (*Salmo salar* Linnaeus, 1758), acclimation to the combination of warm temperature and overnight hypoxia resulted in increased lamellar height, which is another proxy for gill diffusion area; and it also increased thickness of the compact layer of the myocardium. In Arctic char, only the thickness of the compact myocardium was affected (Anttila *et al.*, 2015). This part of the fish heart receives oxygenated blood from the coronary circulation, in contrast to the spongy myocardium, which does not; thus, this change could increase stroke volume or increase the ability of the heart to contract under hypoxia. Thus, changes at the level of both the gill and the heart may be involved in the observed interaction between high temperature and hypoxic acclimation (Anttila *et al.*, 2015).

In Chinook salmon (*Oncorhynchus tshawytscha* (Walbaum, 1792)), cross-tolerance between hypoxia acclimation and thermal tolerance was detected because CTMax was greatest in the fish reared under hypoxic conditions across multiple developmental stages (Del Rio *et al.*, 2019). In this study, fish were reared from an early developmental stage under the altered conditions and remained in these conditions throughout; therefore, it is not possible to determine whether developmental plasticity or acclimation responses caused these phenotypic effects. Hypoxia tolerance was also assessed in fry; time to LOE in severe hypoxia was significantly shorter in fish reared at warm temperatures than at cool temperatures, regardless of prior hypoxia exposure, indicating reduced hypoxia tolerance with warming. However, these experiments were performed at the acclimation temperature, and thus it is not possible to assess the extent of plasticity in hypoxia tolerance because of the confound with temperature. However, these data clearly show that

Chinook salmon will struggle with the combined effects of high temperature and hypoxia, regardless of prior acclimation to either stressor.

In Murray cod (*Maccullochella peelii* (Mitchell, 1838)) there was no significant effect of either hypoxia or high temperature acclimation on critical oxygen tension (the minimum oxygen level needed to maintain standard metabolic rate), but hypoxic acclimation improved hypoxia tolerance measured as oxygen level at LOE with short-term acclimation (7 days). However, longer acclimation to hypoxia (30 days) reduced hypoxia tolerance, suggesting negative effects of prolonged exposure to this stressor (Gilmore *et al.*, 2019). Together, these data suggest that the ability to acclimate to combinations of high temperature and hypoxia is likely to be dependent on multiple factors, including the species and developmental stage tested and the nature of the thermal and hypoxia exposure.

Summary and recommendations

Across all three experimental designs that have been used for detecting interactive effects on plasticity in response to high temperature and hypoxia, it is clear that the extent of plasticity is highly variable across species and levels of stressor exposure and that compensation is rarely complete. This suggests that beneficial acclimation will have only limited success in buffering fishes against the combination of increased temperature and more frequent exposure to hypoxia that is associated with climate change. One key message from these studies is the importance of taking into account the acute effects of high temperature on the response to hypoxia, and vice versa, if the experimental goal is to assess the extent of plasticity resulting in beneficial acclimation. However, comparisons of acclimated animals without knowledge of the acute effects are still extremely useful if the goal is to assess the potential impacts of climate change on animals, because these studies reveal whether there is likely to be a performance decrement after animals have had the opportunity to acclimate to the new conditions. In addition, some studies measure all phenotypes at a single common set of conditions in acclimated fish (most often under cool, normoxic "control" conditions). This approach does not allow one to assess the full extent of plasticity (Einum *et al.*, 2019), but it at least allows phenotypes to be compared without the confounding effects of acute exposures.

Additional studies of the effects of combined acclimation to hypoxia and high temperatures are clearly needed. However, there are multiple challenges involved in designing such studies. First, we strongly recommend that the acute effects of each stressor on the other be measured to allow the assessment of the extent of plasticity. Second, because the potential combinations of stressor intensity and duration of exposure rapidly become intimidatingly large when designing experiments looking at combined stressors, we suggest that careful attention to environmentally realistic exposures is likely to be valuable. In particular, very few studies of acclimation to these combined stressors have taken into account daily variation in these environmental parameters. Most natural aquatic environments undergo daily fluctuations in both temperature and oxygenation; and single-stressor studies indicate that patterns of environmental variation have important consequences for phenotypic responses (Borowiec *et al.*, 2015), emphasizing the importance of environmentally relevant exposures. Similarly, timescales of exposure are likely to be critical, because several studies have suggested that longer-term exposure to high temperature and hypoxia may have detrimental effects that are not fully captured in laboratory studies of acclimation that proceed for only a few weeks.

Finally, it is important to keep in mind that determining whether a particular response is beneficial is a very difficult task. Ultimately, most of the measurements taken by physiologists are only proxies of fitness, and often rather distant ones at that. More studies that examine more direct correlates of fitness (such as reproductive output) are badly needed to determine whether any of the observed plasticity due to acclimation is truly beneficial in an evolutionary sense. This is particularly critical for measurements such as metabolic rate, because the interactive effects of temperature and hypoxia through metabolism are central to thinking in this area. However, it seems difficult to say, *a priori*, exactly what kind of change in standard metabolic rate as a result of acclimation might be beneficial. In general, it is assumed that reductions in standard metabolic rate relative to the acute effect (*i.e.*, partial or complete compensation) are likely to be beneficial because they may represent cost savings in terms of energy expenditure; but this may come at a cost in terms of ability to process food, or to grow, or to perform other key processes. More experiments investigating the effects of acclimation on metabolic rate and the relationship of these changes to the ability of the organism to perform its ecological functions are clearly needed. Even for tolerance traits, where the likely benefit of increases in tolerance is clear, fish biologists often measure proxies of tolerance such as CTMax for thermal tolerance or time to LOE for hypoxia tolerance. Both of these tests have an endpoint that represents some type of neurological failure, because they are associated with spasm and the inability to maintain posture. In natural environments, fish seldom encounter situations that induce these types of neurological failures (with the possible exception of phenomena such as summerkill), and instead the need to tolerate more chronic high temperature and hypoxic exposures is likely of greater importance. At present, it is difficult to know whether traits such as CTMax are even correlated with these other types of thermal tolerance, and our understanding of these issues for hypoxia tolerance is even worse. In general, the field needs to be clearer about what is being measured when we speak of thermal tolerance or hypoxia tolerance, because the standard measurements provide only one narrow window into the

Biol. Bull. 2022, 243: 149–170

ability of fish to withstand high temperatures and hypoxia. It is not sufficient to say that CTMax "is" thermal tolerance or that time to LOE in hypoxia "is" hypoxia tolerance. This is a trap that is very easy to fall into, but we call for a more nuanced view; this becomes even more important when considering interactive effects of high temperature and hypoxia that may be operating on different timescales.

Evidence for Beneficial Developmental Plasticity

Studies of developmental plasticity can be performed in several ways. Some studies expose fish to altered conditions throughout the life cycle from development to adulthood, which mimics the likely effects of natural environmental exposures. That study design is highly relevant to understanding the resilience of fish to climate change but cannot distinguish between the effects of persistent developmental plasticity and acclimation. Instead, studies that expose fish to altered conditions during development (or even during specific critical times during development) and then return the fish to common conditions until testing at later life stages must be used to separate developmental plasticity from plasticity due to acclimation. A recent systematic review of studies of thermal developmental plasticity in CTMax across multiple taxa of ectotherms found that only 20% of the studies surveyed used designs that allow the detection of persistent developmental plasticity separate from effects of acclimation (Pottier *et al.*, 2022). This suggests that even for studies of single stressors in isolation, more care needs to be taken with study design to establish whether developmental plasticity occurs and to separate it from the effects of acclimation.

Meta-analyses of studies that are able to detect developmental plasticity suggest that the direction and extent of developmental plasticity are highly variable between species and traits (Vagner *et al.*, 2019). For example, temperature-induced developmental plasticity has been found to be beneficial, be deleterious, or have no effect on traits such as thermal tolerance (Chen *et al.*, 2013; Moyano *et al.*, 2017; Spinks *et al.*, 2019; Illing *et al.*, 2020), metabolic rate (Schaefer and Walters, 2010; Donelson *et al.*, 2011; Veilleux *et al.*, 2015), swimming performance (Batty *et al.*, 1993; Johnston *et al.*, 2001; Koumoundouros *et al.*, 2009; Burt *et al.*, 2012), and muscle phenotype (Koumoundouros *et al.*, 2001; Scott and Johnston, 2012). Many of these differences are associated with small but persistent differences in gene expression (Scott and Johnston, 2012; Metzger and Schulte, 2018) that may involve differential expression of key regulatory genes involved in muscle development (Fernandes *et al.*, 2006; Macqueen *et al.*, 2008; Campos *et al.*, 2013). Developmental temperature may also have effects on other behaviors related to swimming performance, such as foraging and predator avoidance (Vagner *et al.*, 2019).

The pervasive but inconsistent effects of developmental plasticity in response to elevated temperatures are evident from a meta-analysis of published studies of developmental plasticity in thermal tolerance, in which the magnitude and direction of plastic effects on CTMax or LT_{50} (the temperature lethal for 50% of the animals) were highly variable and on average did not differ significantly from zero (Pottier *et al.*, 2022). However, one general pattern evident in these data is that the developmental stage at which the organisms are exposed appears to be important. For example, embryonic exposure to high temperature tends to have negative effects on thermal tolerance, while exposure at the juvenile stage tends to have positive effects (Pottier *et al.*, 2022).

As is the case for developmental plasticity in response to altered temperatures, the effects of hypoxia during early development on adult phenotypes are quite variable (Vagner *et al.*, 2019). Early developmental exposure to hypoxia has been shown to have long-term effects on growth (Johnston *et al.*, 2013; Vanderplancke *et al.*, 2015), sex ratios (Shang *et al.*, 2006; Robertson *et al.*, 2014), and, in some species, hypoxia tolerance (Wood *et al.*, 2017). However, both beneficial and deleterious effects are observed, making it difficult to determine whether developmental plasticity in response to hypoxia is likely to provide any buffer against the effects of climate change.

The effects of developmental plasticity are thought to be mediated by a variety of epigenetic processes, although most studies to date have addressed the effects of temperature and have examined only changes in DNA methylation (Fernandes *et al.*, 2006; Navarro-Martín, *et al.*, 2011; Anastasiadi *et al.*, 2017; Burgerhout *et al.*, 2017; Metzger and Schulte, 2017). Similarly, changes in DNA methylation have been detected with early exposure to hypoxia (Grigaltchik *et al.*, 2012; Crispo *et al.*, 2020). Overall, the literature suggests that epigenetic changes may have lasting effects on gene expression of an organism and act as a mechanism underlying developmental plasticity in whole-organism phenotypes, but that these changes are not always beneficial.

One study, in zebrafish (*Danio rerio* (Hamilton, 1822)), has examined cross-tolerance between the effects of developmental temperature on hypoxia tolerance at later developmental stages (Levesque *et al.*, 2019), and no evidence for developmental cross-tolerance was found between these stressors. Similarly, the literature examining the long-term effects of developmental exposure to hypoxia and high temperature in combination is very limited. However, the main general pattern that emerges is that there may be some beneficial effects of warm temperature development, but development in hypoxia often has negative effects. A fully factorial study of the effects of high temperature and hypoxia during development in European sea bass (*Dicentrarchus labrax* (Linnaeus, 1758)) revealed both reversible and non-reversible plasticity of traits (Cadiz *et al.*, 2018). Hypoxia exposure had negative effects on body mass at the larval stage, although these differences did not persist once the animals were returned to control conditions at the juvenile stage. Similarly, developmental hypoxia had long-lasting negative effects on hypoxia tolerance (measured as O_2 at LOE), whereas developmental temperature had no effect on hypoxia tolerance (Cadiz *et al.*, 2018). In an African cichlid (*Pseudocrenilabrus multicolor* (Schöller, 1903)), higher developmental temperatures caused a significant increase in CTMax in adults, but developmental hypoxia had no effect on adult thermal tolerance and there was no interaction between the factors (McDonnell *et al.*, 2019).

An extensive experiment in Chinook salmon examined warm temperature and hypoxic exposure (50% dissolved oxygen) from fertilization to hatch, using a fully factorial design (Del Rio *et al.*, 2021). Hatched larvae were then returned to cool, normoxic (control) conditions until the fry stage. At the alevin stage, routine metabolic rate was depressed to a similar extent by warm development, hypoxic development, and the combination of the two stressors; but these differences were not maintained at the later fry stage, demonstrating evidence of reversible plasticity. However, fry that had developed under warm conditions had greater hypoxia tolerance than fry that had developed under hypoxic conditions, suggesting a beneficial cross-tolerance in response to warm development and negative effects of development in hypoxia. However, whether these observed differences at the fry stage would persist to the adult stage through irreversible plasticity remains unknown and requires further investigation. Taken together, the data from the few available studies suggest that there are limited interactive effects of hypoxia and temperature through developmental plasticity and that the effects may be reversible for some traits. Indeed, many of the detected effects of developmental plasticity do not persist into adulthood. As well, interactive effects may not always be beneficial, and negative consequences for adult phenotypes are particularly evident following developmental exposure to hypoxia.

Summary and recommendations

At present it is difficult to determine whether there is much potential for developmental plasticity to buffer the negative effects of increased temperature and decreased water oxygen as our climate changes, because of the paucity of studies. However, the data so far suggest that the extent of developmental plasticity is likely to be dependent on the species, nature, and timing of the developmental exposure and the specific traits being examined. As is the case for studies of acclimation, careful attention to study design going forward is imperative, and we echo previous calls (Groothuis and Taborsky, 2015) to increase the environmental realism of studies of developmental plasticity and to incorporate environmentally relevant exposures and fluctuating environments. In this context, although it makes it impossible to distinguish the effects of developmental plasticity and acclimation, full life-cycle studies in which the organism is exposed to the combination of stressors across its entire life cycle hold promise for assessing the likely impacts of future environments on fish. Although the advantages and disadvantages of partial life-cycle and full life-cycle tests have long been considered in aquatic toxicology (Ankley and Villeneuve, 2006), this framing has not been widely applied in the context of assessing phenotypic plasticity in response to climate change-relevant stressors. We suggest that careful attention to the choice of timing of exposures is needed in studies going forward.

Evidence for Beneficial Transgenerational Plasticity

It has long been known that parental behavior and physiology can affect offspring phenotypes and performance, and both maternal (Green, 2008) and paternal (Crean and Bonduriansky, 2014) effects have been widely documented. It has generally been assumed that maternally derived factors, including materials such as lipids, hormones, and RNA, drive intergenerational effects, based on the relative contribution of the sperm and egg to the zygote (Mousseau and Fox, 1998). However, recent studies (Jiang *et al.*, 2013) have shown that paternal methylation patterns can be stably inherited, suggesting that maternal factors are not alone in influencing offspring phenotype and that sperm can transfer information to embryos *via* a variety of routes (Curley *et al.*, 2011; Kumar *et al.*, 2013; Crean and Bonduriansky, 2014; Donkin and Barrès, 2018). In general, both intergenerational and transgenerational effects can also be mediated through epigenetic mechanism, such as changes in DNA methylation and histone acetylation. All these mechanisms represent forms of non-genetic inheritance, in which offspring inherit something other than just the DNA sequence from their parents. Many forms of non-genetic inheritance, such as those involving transfer of substances such as lipids in the oocyte, are primarily expected to influence only the next generation, with impacts being expected to dissipate across subsequent generations. Conversely, epigenetic mechanisms, such as DNA methylation, at least have the potential to be stably inherited across generations and, thus, could mediate transgenerational plasticity (Mousseau and Fox, 1998; Badyaev and Uller, 2009; Metzger and Schulte, 2016).

Transgenerational plasticity has been detected in a diverse range of taxa from unicellular eukaryotes (Nowacki *et al.*, 2011) to mammals (Blewitt *et al.*, 2006), but the existence and adaptive significance of phenotypic plasticity mediated by transgenerational inheritance is controversial (Horsthemke, 2018; Perez and Lehner, 2019). The challenge of detecting transgenerational plasticity, particularly when the mother is exposed to the environmental stressor, can be illustrated by considering the reproductive biology of vertebrates (Kovalchuk, 2012). In mammals, exposure of a pregnant female exposes both the F1 (embryo) and F2 (embryonic germ cells) generations to the initial stressor (Skinner, 2008). As a result, demonstrating transgenerational plasticity in cases where the mother is exposed requires

Biol. Bull. 2022, 243: 149–170

characterization of phenotypes in at least the F3 generation, because direct exposure of the embryo cannot be ruled out as the cause of the plasticity. The situation is somewhat more straightforward in fish; however, even in fish, germline cells (F1) develop within the gonads of the F0 generation several hours after fertilization (Kurokawa *et al.*, 2006) and, thus, maternal exposure to altered environments may also result in exposures of the F1 germline. Thus, it is necessary for the phenotype to persist to the F2 generation to detect transgenerational plasticity (Mousseau and Fox, 1998; Jablonka and Raz, 2009; Ho and Burggren, 2010). The need for studies across multiple generations has resulted in the majority of transgenerational plasticity studies in fish using small-bodied fish with short generation times (*e.g.*, sheepshead minnow *Cyprinodon variegatus* Lacepède, 1803) (Salinas and Munch, 2012) and zebrafish (Knecht *et al.*, 2017)) as model organisms; thus, little is known about this type of plasticity in other species of fish.

There are multiple studies that suggest that plasticity across a single generation occurs in a wide range of fish taxa, including those in freshwater (Ho and Burggren, 2010, 2012; Lee *et al.*, 2020; Chang *et al.*, 2021; Penney *et al.*, 2021), estuarine (Salinas and Munch, 2012; Chang *et al.*, 2021; Munch *et al.*, 2021), and marine (Donelson *et al.*, 2012; Shama and Wegner, 2014; Veilleux *et al.*, 2015; Shama *et al.*, 2016; Ryu *et al.*, 2020) environments (for review see Munday, 2014; Donelson *et al.*, 2018). For example, in fish, intergenerational plasticity has been detected in response to parental temperature for aerobic scope (Donelson *et al.*, 2012), growth (Salinas and Munch, 2012; Chang *et al.*, 2021; Munch *et al.*, 2021), body size (Shama and Wegner, 2014), sex ratio (Pierron *et al.*, 2021), and hypoxia tolerance in response to parental exposure to hypoxia (Ho and Burggren, 2012; Ragsdale *et al.*, 2020). Studies across multiple generations (demonstrating transgenerational plasticity) are rarer, but beneficial effects of elevated grandparental temperature on juvenile growth across two generations have been detected in sheepshead minnows (*C. variegatus*), threespine stickleback (*Gasterosteus aculeatus* Linnaeus, 1758), and spiny chromis damselfish (*Acanthochromis polyacanthus* (Bleeker, 1855)) (Shama and Wegner, 2014; Donelson *et al.*, 2016; Lee *et al.*, 2020). In contrast, hypoxia exposure has been shown to have negative effects on reproductive fitness across several generations (Wang *et al.*, 2016; Lai *et al.*, 2019). For example, hypoxia causes female marine medaka (*Oryzias melastigma* (McClelland, 1839)) to alter DNA methylation and gene expression patterns and is associated with a dramatic decrease in hatching success through to the F2 generation (Lai *et al.*, 2019).

A meta-analysis of transgenerational plasticity across both plants and animals for a variety of environmental exposures and phenotypes suggests that the mean effect size for transgenerational plasticity is not distinguishable from zero, with both positive and negative plasticity being detected, depending on the study (Uller *et al.*, 2013). This pattern suggests that beneficial transgenerational plasticity is not a general phenomenon and may be present only in a subset of species or under very specific conditions (Kovalchuk, 2012). For example, spiny chromis damselfish demonstrate beneficial transgenerational plasticity in aerobic scope (a proxy for performance and fitness) with warming of +1.5 °C, whereas fish warmed at +3.0 °C displayed reduced aerobic scope (Donelson *et al.*, 2016). These observations are consistent with the idea that high-intensity stress is less likely to lead to adaptive plasticity compared to familiar, moderate-intensity stress (Parsons, 1994, 2005). The total length of exposure can also strongly influence whether beneficial transgenerational plasticity is detected. For example, sheepshead minnows required at least 30 days of exposure to elevated temperatures (+10 °C) to show beneficial transgenerational plasticity, whereas shorter parental exposures had no effect (Salinas and Munch, 2012).

The adaptive significance of transgenerational or intergenerational plasticity, if present, is likely to be dependent on the extent to which the environmental conditions of the parental generation predict the environment that will be experienced by future generations. This idea has strong empirical support from studies in sheepshead minnows (Munch *et al.*, 2021). In this species, individuals from less predictable environments exhibited less plasticity across generations than individuals from more predictable environments (Munch *et al.*, 2021). These observations are consistent with the hypothesis that transgenerational plasticity is generated only under a very particular set of circumstances that are likely to vary across species.

There are very few, if any, studies of transgenerational effects of combinations of hypoxia and temperature (Donelson *et al.*, 2018). One study has examined the potential for transgenerational cross-tolerance between these stressors and found that exposing the parental generation of zebrafish to hypoxia leads to increased hypoxia tolerance in offspring but does not significantly affect thermal tolerance, indicating an absence of transgenerational cross-tolerance (Ho and Burggren, 2012). More studies of combined stressor exposures and cross-tolerance are needed to allow assessment of the potential for transgenerational plasticity to act to increase the resilience of fishes to climate change.

Conclusions and Implications

Although studies of the extent of plasticity in fishes in response to exposure to the combination of high temperature and hypoxia are relatively rare, it is clear that most fish have only limited capacity to compensate for the synergistic negative effects of acute exposure to these stressors. In particular, cross-tolerance responses appear to occur under only a relatively narrow range of circumstances and only in a few species. Thus, this type of within-generation plasticity is likely to have only limited utility for buffering fishes in the face of climate change, particularly at species' range edges, where available plastic responses may already be recruited to cope with current conditions. However, our ability to make strong conclusions about the likely benefit of acclimation responses is limited by the relatively small number of studies in which both acute and acclimated phenotypes have been assessed, which makes assessing the extent of phenotypic plasticity impossible. The limitations on plasticity are hinted at, however, by comparisons of animals acclimated to future conditions that suggest the presence of ongoing negative impacts of exposure to high temperature and hypoxia that cannot be fully compensated.

Developmental plasticity seems even more unlikely to provide significant compensatory effects. In general, there is some evidence for beneficial developmental plasticity in response to either hypoxia or temperature alone, although hypoxic exposures during development also often have deleterious effects. Combined exposures have rather variable effects, depending on the species and the exposure conditions; and the detrimental effects of hypoxic exposure may undermine any beneficial effects of development at warmer temperatures. To properly assess the extent of developmental plasticity and distinguish these effects from the effects of acclimation, it is necessary to expose fish to altered conditions during development and then return them to control conditions until phenotypes are assessed at subsequent life stages. However, in the context of climate change, fish are much more likely to be exposed to altered conditions during both development and subsequent life stages. There are very few studies that have examined these types of life-cycle exposures to assess the possibility of combinations of developmental plasticity and acclimation to increase resilience in the face of climate change. The intergenerational and transgenerational effects of exposure to combinations of hypoxia and high temperature are largely unknown, and studies of this sort are desperately needed to understand the likely impacts of climate change on fishes.

Although this assessment paints a rather bleak picture of the potential for phenotypic plasticity (at any timescale) to fully protect fish populations from either the gradual increases in temperature and hypoxia or the increased frequency of extreme events, there is also substantial between-individual variation in plasticity in fish (Seebacher and Little, 2021), as well as interindividual variation in tolerance of both high temperature and hypoxia (Strowbridge *et al.*, 2021). Thus, it is possible that our changing climate will impose selection on this standing genetic variation that may provide some resilience of fish populations in the face of combined exposures to high temperature and hypoxia as our climate changes.

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