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Review

Stress responses in fish: From molecular to evolutionary processes

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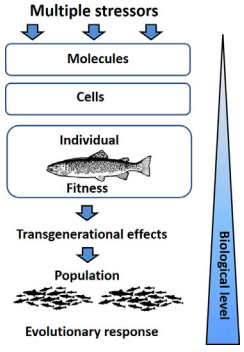
HIGHLIGHTS

- Multiple stressors have cascading effects from molecules to fish populations.
- Fish can switch from a "compensation" to a "conservation" metabolic strategy.
- This can lead to synergistic or antagonistic effects of multiple stressors.
- Transgenerational plastic, genetic and epigenetic effects are frequent.
- This can lead to local adaptation and evolutionary changes at the population level.

GRAPHICAL ABSTRACT



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ABSTRACT

In the context of global changes, fish are increasingly exposed to multiple stressors that have cascading effects from molecules to the whole individual, thereby affecting wild fish populations through selective processes. In this review, we synthetize recent advances in molecular biology and evolutionary biology to outline some potentially important effects of stressors on fish across biological levels. Given the burgeoning literature, we highlight four promising avenues of research. First, (1) the exposure to multiple stressors can lead to unexpected synergistic or antagonistic effects, which should be better taken into account to improve our predictions of the effects of actual and future human activities on aquatic organisms. Second, (2) we argue that such interactive effects might be due to switches in energy metabolism leading to threshold effects. Under multiple stress exposure, fish could switch from a "compensation" strategy, i.e. a reallocation of energy to defenses and repair to a "conservation" strategy, i.e. blocking of stress responses leading to strong deleterious effects and high mortality. Third, (3) this could have cascading effects on fish survival and population persistence but multiscale studies are still rare. We propose emerging tools merging different levels of biological organization to better predict population resilience under multiple stressors. Fourth (4), there are strong variations in sensitivity among populations, which might arise from transgenerational effects of stressors through plastic, genetic, and epigenetic mechanisms. This can lead to local adaptation or maladaptation, with strong impacts on the evolutionary trajectories of wild fish populations. With this review, we hope to encourage future research to bridge the gap between molecular ecology, ecotoxicology and evolutionary biology to better understand the evolution of responses of fishes to current and future multiple stressors in the context of global changes.

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Contents

1. Introduction . . . 372
1.1. Definitions and objectives . . . 372
2. Interactive effects of multiple stressors . . . 372
3. Metabolic strategies in response to multiple stressors . . . 373
4. Cascading effects of stressors from molecules to populations . . . 374
5. Population variability and evolutionary effects of stressors . . . 376
6. Conclusion . . . 378
Acknowledgements . . . 378
References . . . 378

1. Introduction

Due to global changes, wild fish populations are exposed to multiple environmental stressors, such as global warming, pollution or emerging pathogens, which have attracted a number of exciting research questions in the last decades (Woodward et al., 2010; Crozier and Hutchings, 2014; Schulte, 2014; Matthaei and Lange, 2016; Lange et al., 2018). For instance, what are the consequences of multiple environmental stressors on fish at the molecular, physiological and whole organism levels? How are stress responses integrated across levels of biological organization, especially under multiple stressors? Why are some populations able to cope with environmental stressors while some others dwindle? What are the long-term consequences of stressors across generations and the evolutionary mechanisms involved?

To address these questions, a large body of research has been dedicated to the molecular and physiological pathways involved in the stress response, with a rise in the literature focusing on fish in the last decades (Barton, 2002; Killen et al., 2013; Schulte, 2014; Schreck et al., 2016; Balasch and Tort, 2019). In parallel, other studies have focused on the evolutionary mechanisms explaining phenotypic and genetic divergence across fish populations exposed to different levels of perturbations (Crozier and Hutchings, 2014; Reid et al., 2016; Whitehead et al., 2017), leading to the emerging field of evolutionary ecotoxicology (Bickham, 2011; Coutellec and Barata, 2011; Oziolor et al., 2016, 2017; Brady et al., 2017a). However, much remains to be done to bridge the gap between studies examining the impacts of multiple stressors on cells and organisms and studies examining the evolutionary causes of variations in genotypes and sensitivity across populations. This is partly because different fields of biology (e.g. molecular ecology, ecotoxicology, ecophysiology, evolutionary biology) have developed different approaches. In this review, we attempt to build on recent advances in molecular and evolutionary ecology to give a synthetic view of the evolution of stress response in fish across levels of biological organization.

1.1. Definitions and objectives

The stress response per se (i.e. the physiological response triggered by stressors) is a complex series of biochemical, physiological and behavioral adjustments to environmental variations, that can enable the maintenance of internal homeostasis and survival under some conditions (Bonga, 1997; Chrousos, 1998; Barton, 2002). Stress responses can also have negative long-term consequences depending on the level/duration/number of stressors (Schulte, 2014; Balasch and Tort, 2019). Some stress responses are mediated by changes in stress hormones levels (catecholamines and glucocorticoids, especially cortisol), while some responses are directly mediated by the stressor itself, for instance temperature-inducible molecular changes in Heat Shock Proteins (HSP) or stress-induced epigenetic changes (Iwama et al., 1998; Feil and Fraga, 2012; Schulte, 2014; Rey et al., 2016; Schreck et al., 2016). We will here adopt a broad definition of stress responses and consider responses that are initiated by stress hormones or directly by the stressor itself, following the definition given in Schulte (2014). We chose this broad definition of stress responses for two reasons. First, some mechanisms underpinning some stress-induced behavioral, reproductive or morphological changes are still unknown. Second, there is now recent evidence that direct effects of stressors play a larger role than previously thought, for instance through epigenetic changes (e.g. Rey et al., 2016).

Interestingly, empirical studies bring contrasted results depending on the species, population, and stressor(s), making it difficult to predict the responses of aquatic organisms in their natural environment (Lavergne et al., 2015; Pédron et al., 2017a, 2017b; Attard et al., 2018). In this review, we synthetize recent advances in molecular biology (especially omics approaches) and evolutionary ecotoxicology. We focus on abiotic thermal (changes in temperature) and chemical stressors (contaminants and more generally, altered water quality), because they are of increasing concern in wild and farmed fish populations due to global changes (Schinegger et al., 2012, 2018). We also include biotic stressors such as predators and parasites because they are also affected by global changes (e.g. invasive predators and emerging diseases) (Rahel and Olden, 2008; Altizer et al., 2013; Cable et al., 2017) and because they can interact with abiotic stressors (Thilakaratne et al., 2007; Blanar et al., 2009; Marcogliese and Pietrock, 2011; Schmitz et al., 2016). However, the combined effects of multiple biotic and abiotic stressors on fish across levels of biological organization are still poorly known (Jackson et al., 2015; Schinegger et al., 2016). This highlights the need of multiscale studies from molecules to populations to better understand their effects on aquatic organisms.

Based on the existing literature, we propose four promising avenues of future research. We first (1) propose that exposure to multiple stressors results in complex interactive effects (synergism or antagonism) across biological scales, which need to be taken into account in future studies. Second, (2) we suggest that such effects might result from switches from a "metabolic compensation strategy" to a "metabolic conservation strategy", when a certain threshold or combination of stressor (s) is reached, resulting in contrasted deleterious effects at higher levels of biological organization. Third, (3) we expose how this might differentially affect individual fitness and population persistence, potentially explaining why some populations resist to perturbations while others dwindle. Fourth, (4) we then review evidence of demonstrated inter-population variability in fish stress responses and expose how transgenerational effects of stressors could have strong consequences for the evolutionary trajectories of wild populations, leading in some cases to extinction or to local adaptation. We believe that developing such promising avenues of future research will significantly enhance our understanding of fish response to current and future stressors in the context of global changes (Table 1).

2. Interactive effects of multiple stressors

Most existing studies focus on the effect of one specific stress factor in isolation. Due to multiple anthropogenic activities and global changes, aquatic organisms are however often exposed to several stressors at once (Matthaei and Lange, 2016; Schinegger et al., 2016,

Table 1
Summary of promising questions and future prospects.

Question 1: What are the effects of multiple abiotic and biotic stressors across biological levels? Are synergic or antagonistic effects more frequent than previously thought?
Current limitations and future prospects: Multiple stressors can have unexpected synergistic or antagonistic interaction effects on fish depending on the level of biological organization considered. Empirical studies in semi-controlled conditions from molecules to populations will help unraveling such interaction effects.
Question 2: What can explain these interactions effects? Are different metabolic strategies set up under single vs. multiple stressors?
Current limitations and future prospects: The metabolic strategy framework (compensation vs conservation strategy, sensu Sokolova, 2013) is a powerful framework for a better understanding of the high variability of stress responses observed in wild populations. Fish could switch from a "compensation" to a "conservation" metabolic strategy when exposed to multiple stressors, with contrasted effects across biological levels (Fig. 1). More empirical studies are needed to test this promising theoretical framework.
Gandar, 2015Gandar, 2015vGandarQuestion 3: What are the consequences on individual fitness and population persistence? Are there emerging tools to better link different levels of biological organization, from molecules to populations?
Current limitations and future prospects: Most studies have focused on molecular pathways involved in the stress response while other studies compared individual fitness and population dynamics across environments. Integrated biomarkers and theories linking molecular and population effects could be powerful tools to bridge the gap between small- and large-scale effects of environmental stressors (Fig. 2).
Question 4: Why do different populations differ in their sensitivity to stressors? Can local adaptation occur and which evolutionary processes are involved (genetic, plastic, epigenetic effects)?
Current limitations and future prospects: Molecular studies have enhanced our understanding of genetic and epigenetic processes underpinning adaptive processes, but they have been rarely applied to wild populations exposed to stressors. Future studies tracking molecular, genetic and epigenetic changes among stressed and unstressed fish populations while taking into account their evolutionary history will give insight into the evolutionary potential of wild fish populations exposed to multiple global changes.

2018). Evaluating these multistress effects remains however a challenge: complex interactions between stressors can be expected, because different kinds of stressors trigger different physiological pathways that can interfere (Killen et al., 2013; Segner et al., 2014). Experimental studies using specific combinations of stress factors have for instance unveiled complex interactive effects of thermal, toxic or biotic stressors (Marcogliese et al., 2005; Holmstrup et al., 2010; McBryan et al., 2013; Gandar et al., 2017a, 2017b; Pédron et al., 2017a), resulting in different types of interactions between stressors (Folt et al., 1999; Christensen et al., 2006; Côté et al., 2016; Liess et al., 2016).

Synergism occurs when individuals exposed to a stressor have a lower resistance or tolerance to another stressor (Liess et al., 2016; Lange et al., 2018). For instance, an increase in temperature can amplify the deleterious effects of contaminants, because increased temperature can increase metabolic rates and assimilation of contaminants in fish (Noyes et al., 2009). In addition, thermal stress can disrupt the ability of fish to set up an adequate stress response, thereby impairing their ability to limit the deleterious effects of contaminants (Kennedy and Ross, 2012; Gandar et al., 2015, 2017b). Inversely, the metabolic costs of pollutant exposure may disturb the molecular and physiological processes involved in thermal acclimation (Gordon, 2005; López-Olmeda and Sánchez-Vázquez, 2011). In these cases, synergism between stressors can be expected. As a consequence, more severe deleterious effects at the cell and individual levels can be observed under multiple stressors compared to single stressors with potential important negative consequences for fish survival and population persistence in the wild. For instance, pesticides have a higher negative effect on goldfish *Carassius auratus* when they are combined with a thermal stress (Gandar et al., 2017a, 2015, 2017b; Jacquin et al., 2019).

On the opposite, *antagonism* occurs when exposure to one stressor limits or decreases the effects of another stressor (Folt et al., 1999; Jackson et al., 2015), especially when physiological adaptations to one stressor are beneficial against the exposure to additional stressors (e.g. co-tolerance) (Vinebrooke et al., 2004). For instance, some families of Atlantic salmon *Salmo salar* that are tolerant to high-temperature are also more tolerant to hypoxia, because of increased heart ventricle size and myoglobin levels (e.g. Anttila et al., 2013). Fish are also interacting with natural stressors and a number of other species (predators, parasites) in their environment, which may also change the outcomes of stressor exposure (Holmstrup et al., 2010). For instance, a growing number of studies showed that fish exposed to contaminants are more susceptible to predation due to neurotoxic effects and disruption of social interactions by pollution (e.g. Lurling and Scheffer, 2007; Tudorache et al., 2008). In addition, fish exposed to contaminants can be more susceptible to parasitism. For instance, Nile tilapia *Oreochromis niloticus* exposed to contaminated sediments have more gill monogean parasites due to immunosuppressive effects of toxicants (Sanchez-Ramirez et al., 2007). Conversely, parasitism can increase the sensitivity of hosts to pollutants in three-spined sticklebacks *Gasterosteus aculeatus* (Pascoe and Cram, 1977). Thermal stress can also have strong effects on host-parasite interactions. For instance, the occurrence and negative effects of the emerging Proliferative Kidney Disease (PKD) on brown trout *Salmo trutta* are increased by water warming, with dramatic consequences for European salmonid populations (Okamura et al., 2011; Bruneaux et al., 2017).

Experimental studies manipulating the composition of communities, and field studies evaluating these multiple stress effects with realistic biotic interactions should now be conducted to refine our ability to predict the effects of future stressors on aquatic wildlife (Hahn, 2011).

3. Metabolic strategies in response to multiple stressors

Recent studies help unraveling the underpinning mechanisms explaining these complex multiple stressor effects. During the last decade, a growing body of research used "omics" tools, providing new insights into physiological pathways involved in fish stress responses (Gonzalez and Pierron, 2015; Oziolor et al., 2017). These "omics" methods have been applied at different levels of biological organization (i.e. genomics, transcriptomics, proteomics, metabolomics) to evaluate the response of fish to temperature (e.g. Kullgren et al., 2013; Bermejo-Nogales et al., 2014; Yang et al., 2016), altered water quality and pollution (e.g. Li et al., 2016; Oziolor et al., 2017; Ortiz-Villanueva et al., 2018), pathogens (e.g. Lü et al., 2014), and recently to multiple stressors (Gandar et al., 2017b; Pédron et al., 2017a). Although response patterns can vary according to the species and the nature, intensity or duration of stressors, most studies highlight the central role of defense systems and metabolism (Kassahn et al., 2009). More specifically, stress responses generally involve changes in defense systems (e.g. chaperone proteins HSP, antioxidant systems, immunity), and more importantly, energy metabolism (e.g. Evrard et al., 2013; Bermejo-Nogales et al., 2014; Gandar et al., 2015, 2017b; Naour et al., 2017). For instance, a transcriptomic approach showed that most transcript changes of delta smelt *Hypomesus transpacificus* exposed to salinity stress are related to metabolic processes (Komoroske et al., 2016). Naour et al. (2017) also showed that stressed red cusk-eel *Genypterus chilensis* have altered expression levels of energy metabolism pathways, especially gluconeogenesis, triacylglyceride catabolism, cholesterol and fatty acid biosynthesis.

More generally, under single stressor exposure, energy and oxygen consumption is generally increased to face the cost of stress response, as shown in bluegill sunfish *Lepomis macrochirus* exposed to wastewater effluents (Du et al., 2018). However, responses to multiple stressors are often very different compared to single stressors. For instance, goldfish exposed to multiple thermal and toxic stressors show on the contrary a decrease of energy consumption, a decrease of amino acid metabolism, energy production and defense systems (Gandar et al., 2017a). Metabolism and the regulation of energy balance are thus central in the understanding of (multi)stress responses (Kassahn et al.,

2009). Below we propose a theoretical framework based on metabolic strategies proposed by Sokolova et al. (2012) and Sokolova (2013), to better predict the impacts of single vs. multiple stressors across levels of biological organization.

The tolerance to environmental stressors depends largely on the energy available, the efficiency of acquisition and conversion of food, but also on the ability to mobilize energy resources to compensate for the metabolic cost of defenses (Sokolova et al., 2012; Sokolova, 2013). The constraint of maintaining the aerobic metabolic capacity determines the stress tolerance of organisms and therefore their chances of survival (Kassahn et al., 2009). In addition, the bioenergetic costs of maintaining homeostasis and defense systems while repairing damages increase with the intensity and number of stressors, and this can lead to different metabolic strategies and result in strong threshold effects (Sokolova et al., 2012). In other words, the effects of stressors are very different depending on the duration, dose and combinations of stressors because alternative metabolic strategies can be displayed. Below, we describe the two main types of metabolic responses and the associated physiological effects that can be expected under single vs. multiple stressors (Fig. 1).

Specifically, when the dose, duration and/or number of stressors is low, fish might display a "*metabolic compensation*" strategy (sensu Sokolova, 2013). Fish implement a complete stress response from molecules to the whole individual. In a nutshell, cortisol and catecholamine levels are increasing, leading to the reallocation of energetical resources to defense mechanisms and maintenance (e.g. detoxification, immunity, damage repairs), which enables maintaining homeostasis and survival. For instance, stressed gilthead sea bream *Sparus aurata* show increased mitochondrial metabolism (Bermejo-Nogales et al., 2014) and goldfish exposed to single stressor (thermal or toxic stressor alone) show increased energy consumption and oxidative defenses (Gandar et al., 2017a). Because the energy demand for maintenance increases, the energy available for growth, reproduction, activity and storage of reserves decreases (Sokolova, 2013) (Fig. 1). This can lead to a temporary reduction in body mass, growth and/or reproduction. For instance, fathead minnows *Pimephales promelas* exposed to temporary anthropogenic pollution in urban streams show reduced egg production (Crago et al., 2011). However, negative long-term consequences of single stressors for fitness might be reduced, if defense and repair mechanisms have been efficiently mobilized, thereby reducing long-term irreversible cellular damage and mortality in the long term (Fig. 1). Accordingly, goldfish exposed to single thermal or toxic stressor alone show limited irreversible cellular damage in their gills and liver, which may ensure long-term survival (Jacquin et al., 2019). This is a "*metabolic compensation*" strategy where the energy is allocated to stress resistance, allowing the organism to efficiently face stressors with limited long-term damage. In this case, strong short-term changes in metabolism, immune and anti-oxydant defenses might be observed at the molecular and physiological level, but with low damage at the cellular level. At the individual level, this could translate into low effects on mortality and fish fitness can be temporarily maintained (Fig. 1). Long-term studies in wild populations are however needed to formally test these fitness effects.

In contrast, when the dose, duration and/or number of stressors is high, fish could display a "*metabolic conservation*" strategy (sensu Sokolova, 2013) (Fig. 1). In such conditions, the energy demand for maintenance might be too high (i.e. beyond the aerobic metabolic capacity of the fish), or there might be a disruption of aerobic metabolism, leading to a decrease in the energy available below the energy demand (Sokolova et al., 2012). In both cases, aerobic metabolism cannot cover the energy demand. Metabolism can then switch to partial anaerobic to cover the costs of maintenance. Organisms can then enter into a state of "*metabolic shutdown*", i.e. a suppression of all metabolic activity above basal metabolism, a decreased catabolism of carbohydrates and amino acids. This phenomenon, called a "*conservation strategy*" (Sokolova et al., 2012, Sokolova, 2013), has been observed under multiple stress exposure. For instance, gilthead seabream exposed to multiple stressors (water level changes and chasing) show a blocked stress response (no cortisol increase) and a switch from aerobic to anaerobic metabolism (Bermejo-Nogales et al., 2014). Because stress responses are blocked and defense systems are not triggered, no effects on routine behaviors and growth and reproduction are expected (Fig. 1). However, strong deleterious effects on cellular structure (high levels of cellular lesions and DNA damage) can be expected. For instance, goldfish conjointly exposed to high temperature and pesticides show reduced metabolism associated with increased cellular lesions of the gills and liver (Gandar et al., 2017a, 2017b; Jacquin et al., 2019). This can then translate into high mortality and low fitness, with potential detrimental effects for population persistence (de Montaudouin et al., 2010). However, empirical studies testing the long-term effects of these "*compensation*" vs "*conservation*" metabolic strategies on fish fitness and populations are now needed to formally test these hypotheses.

Taken together, the existing studies show that the stress tolerance and long-term effects of stressors largely depends on the energy balance and metabolic capacity of the fish, especially in a multistress context. However, the specific stimuli triggering a switch from a "*compensation*" to a "*conservation*" metabolic strategy remain to be determined. Identifying the thresholds and combinations of stressors leading to each metabolic strategy is a major challenge for future research. To tackle this question, we need more empirical studies in realistic ecological conditions to better understand when and how the physiological endpoints of individuals are reached, and to help refining environmental risks posed by multiple anthropogenic stressors.

4. Cascading effects of stressors from molecules to populations

As explained above, exposure to single vs multiple stressors thus have strong consequences across levels of biological organization, depending on the metabolic strategy adopted, with potentially strong consequences for population persistence. However, most existing studies focused on the molecular and cellular levels, and less work is devoted to the population level. Here we highlight some potential effects of damage induced by single vs multiple stressors on individual fitness and population persistence (Fig. 2).

As seen above, exposure to moderate and/or single stressors is expected to lead to a "*compensation*" metabolic strategy (Sokolova, 2013), resulting in limited oxidative and cellular damage (Fig. 1). This is because Reactive Oxygen Species (ROS) induced by moderate/single stressors (Malek et al., 2004; Slaninova et al., 2009; Lushchak, 2011; Cui et al., 2014), might be rapidly neutralized via the anti-oxidant and repair machinery that is fully triggered under a compensation metabolic strategy (Fig. 1). This is expected to result in limited irreversible damage to DNA, cells and organ functions and low effects on individual survival and fitness (e.g. Gandar et al., 2015; Jacquin et al., 2019). If individuals can maintain their long-term fitness under single or moderate stress conditions, one can expect a low risk of population extinction on the long term (e.g. de Mautaudoin et al., 2010).

In contrast, under multiple stressors, individuals often display a "*conservation*" metabolic strategy which leads to a metabolic shutdown blocking the anti-oxydant and repair machinery (Fig. 1). Excessive oxidative stress under multiple stress exposure can lead to irreversible DNA and cell damage (Valavanidis et al., 2006; Raphael et al., 2014; Santos et al., 2017), with potential impacts for organ function, fish survival and fitness (Costa et al., 2011; Xing et al., 2012; Birnie-Gauvin et al., 2017). Amplified negative effects of multiple stressors are thus expected on fish survival (Wang et al., 2017). This might have severe consequences for population persistence for at least two reasons.

First, alterations of cell structure and cycle (through activations of the tumor protein p53 for instance) can lead to enhanced cancer risk (Hagenaars et al., 2013; Topal et al., 2014), as shown in zebrafish *Danio rerio* exposed to multiple pesticides (Weber et al., 2013) or in goldfish exposed to increased temperature and pesticides levels (Gandar et al., 2017b). At the population level, this could lead to

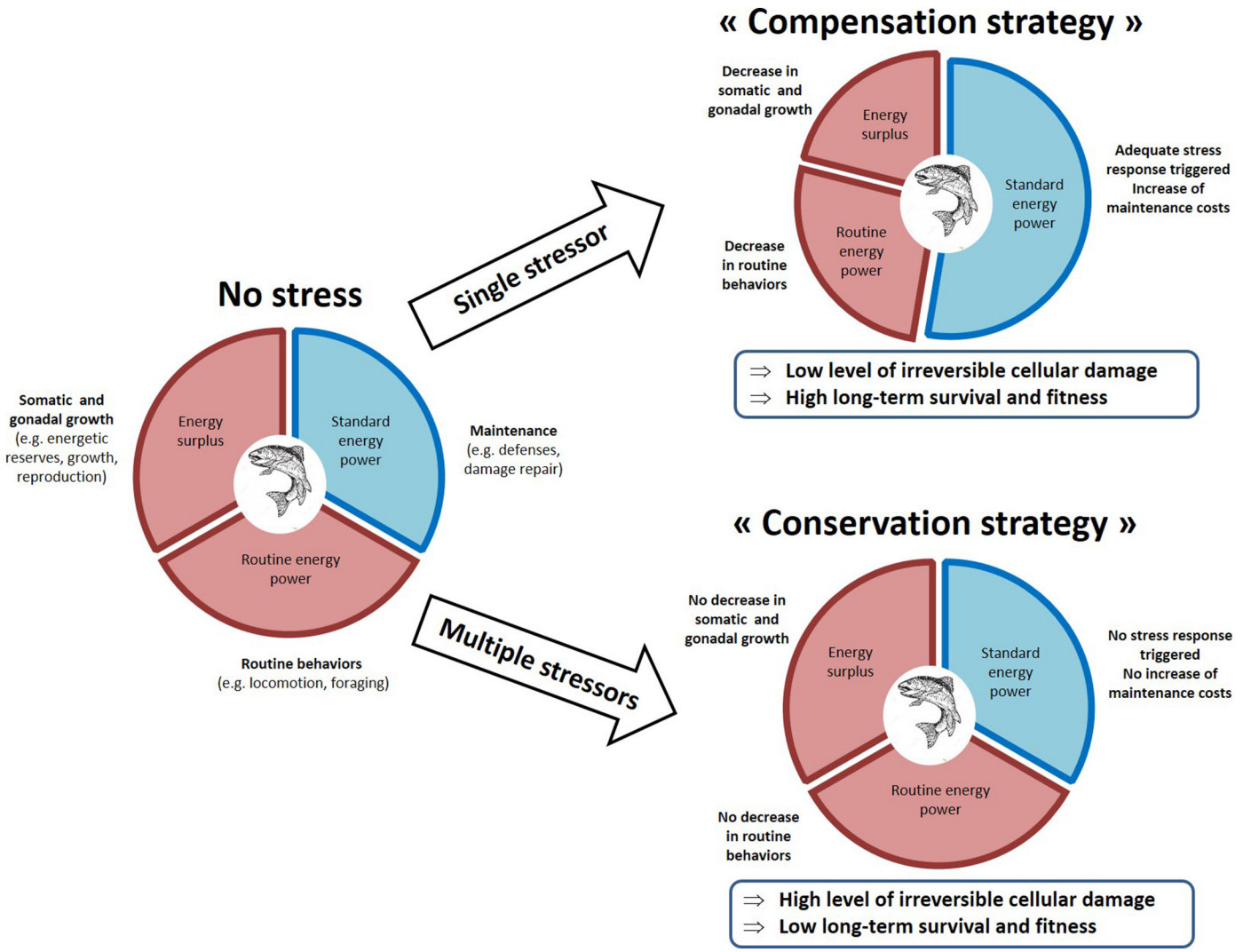

Fig. 1. Schematic representation of theoretical allocation of energy following the concept of metabolic capacity of Fry (1947) and metabolic strategies of Sokolova (2013). Under normal conditions (no stress, on the left), the total energy available (represented by the circle) is first allocated to maintenance and damage repair (standard energy power), then to routine behaviors (locomotion, foraging). The energy surplus is invested in somatic and/or gonadal growth (growth and reproduction). Under exposure to a single stressor, a "compensation strategy" response is observed: the energy allocated to maintenance increases, at the expense of routine behaviors, and growth. This stress response usually leads to limited irreversible damage to cells and tissues, and low fitness effects. Under multiple stressors exposure, the energy available might be insufficient to cover the costs of maintenance, leading to a "conservation strategy": the stress response is blocked and no reallocation of energy is observed. In this case, high level of irreversible cellular damage is expected, with increased mortality and deleterious effects on fitness.
(Adapted from Sokolova, 2013, Gandar et al., 2015).

increased cancer prevalence and high extinction risk in fish populations exposed to multiple environmental stressors (Baumann, 1984, 1998; Black and Baumann, 1991), although more empirical studies are necessary to unravel the complex interactions between individual and environmental determinants of cancer occurrence and extinction in wild populations (Hochberg and Noble, 2017; Vittecoq et al., 2018).

Second, excessive oxidative stress observed under multiple stressors can affect DNA structure and integrity (Cachot et al., 2006; Polard et al., 2011; Santos et al., 2017). In some cases, this can lead for instance to accelerated attrition of telomeres that are non-coding, repetitive sequences located at the ends of chromosomes, protecting them during replication. Individuals that have stress-shortened telomeres have accelerated senescence, and diminished longevity (Bize et al., 2009; Herborn et al., 2014; Bernadotte et al., 2016; Reichert and Stier, 2017). Interestingly, environmental stressors such as heat stress and pollutants have been shown to increase telomere attrition in various vertebrates including fish (Boonekamp et al., 2014; Blévin et al., 2016; Debes et al., 2016; Simide et al., 2016; McLennan et al., 2017; Angelier et al., 2018), and this has been associated with enhanced extinction risk at the population level (Dupoué et al., 2017). Integrative markers such as telomeres could thus be highly relevant because they integrate stressors effects from molecules to populations and help anticipating the extinction risks of wild fish populations exposed to multiple stressors.

Ultimately, predicting the emerging properties of aquatic systems exposed to multiple stressors would need more integrative approaches to better anticipate extinction risk at the population level. Biological systems respond to multiple perturbations as multiple-level interactions, within networks of cellular traits, connected physiological processes and interspecies interactions (Geist, 2011; Segner et al., 2014; Balasch and Tort, 2019). Theoretical frameworks examining the dynamics of cellular to organismal and population extinction risk have been proposed (Connon et al., 2012). For instance, synthetic biology (Kitano, 2002) or the Adverse Outcome Pathways (AOP) assessment aims to establish associations between different levels of biological organization and ultimately on population extinction risk (Ankley et al., 2010). This methodology has been applied to high-density transcription data in fathead minnows, to relate chemical exposure to disruption of the hypothalamus-pituitary-gonadalendocrine pathway leading to reprotoxic effects and decreased reproduction in fish populations (Perkins et al., 2011). However, empirical data on population dynamics and extinction risk are still lacking to fully implement such methodologies under (multi)stress exposure and to better integrate the evolutionary responses of stressed wild populations.

5. Population variability and evolutionary effects of stressors

Interestingly, a growing number of studies highlights a high variability in sensitivity to stressors among wild fish populations exposed to contrasted environmental conditions. For instance, different populations of European flounder *Platichthys flesus* present different sensitivities to temperature, hypoxia and contamination (Lavergne et al., 2015; Pédron et al., 2017b). Wild guppies *Poecilia reticulata* evolving under contrasted PAHs pollution regimes in Trinidadian rivers have different morphology and behaviors (Rolshausen et al., 2015; Jacquin et al., 2017). Atlantic killifish *Fundulus heteroclitus* living in industrially polluted sites show enhanced pollution tolerance, indicating rapid adaptation to extreme pollution (Reid et al., 2016; Whitehead et al., 2017). Such examples have led to the rise of the emerging field of evolutionary toxicology, which is a promising route towards a better understanding of long-term population responses to environmental stressors (Bickham, 2011; Coutellec and Barata, 2011; Brady et al., 2017b; Hamilton et al., 2017; Oziolor et al., 2017), while raising some exciting challenges for future research. For instance, the observed population divergence can sometimes result in adaptation (enhanced fitness) or to maladaptation (decreased fitness) in stressful environments, and the conditions in which adaptive divergence occurs are not clear yet (Loria et al., in press; Ghalambor et al., 2007; Merilä and Hendry, 2014). In addition, the evolutionary mechanisms leading to divergence among populations are still debated, because genetic, plastic and epigenetic processes often interact to shape their evolutionary trajectories (Merilä and Hendry, 2014; Merilä, 2015; Beaman et al., 2016) (Fig. 2). We discuss some of these mechanisms below.

Under some conditions, genetic local adaptation can occur. Due to selective and neutral processes, some specific resistant genotypes can be fixed in natural populations exposed to stressors, leading to local adaptation, i.e. enhanced fitness in stressful environments. However, empirical evidence of such genetic-based local adaptation in fish is still scarce. One of the best documented example is the killifish (e.g. Oziolor et al., 2014; Reid et al., 2016). *Fundulus heteroclitus* living in urban estuaries show strong genetic variations in toxicity mediating genes (such as the aryl hydrocarbon receptors AHR) which confer them a high tolerance to normally lethal levels of pollution (Reid et al., 2016; Whitehead et al., 2017). Interestingly, different populations having evolved in different sites show distinct molecular variations in genes connected to signaling and detoxification pathways. This suggests that different genetic combinations might have been selected for to confer the same adaptive tolerance in different killifish populations (Reid et al., 2016). High standing genetic diversity is thus crucial to determine the evolutionary potential of fish populations exposed to stressors.

One major challenge is however to predict the evolutionary responses to multiple stressors. For instance some genetic adaptations might confer advantages against additional stressors, such as in some *Daphnia magna* populations co-adapted to warming and increased toxicity (Zhang et al., 2018). In other cases, adaptation to one stressor might impede adaptation to another stressor, such as in European flounder populations exposed to contamination that are less able to respond to thermal stress (Lavergne et al., 2015). Modelling approaches might help determining the effects of multiple environmental stressors on selective processes and population extinction risk. For instance, an individual-based demo-genetic model predicted the combined effects of river flow and ocean warming on salmon population resilience and genetic evolution (Piou and Prévost, 2013).

In addition, plasticity and transgenerational plasticity (parental effects) are major drivers of rapid phenotypic divergence among populations under stress exposure, because they can enable individuals with a given genotype to rapidly adjust their phenotypes to environmental conditions (Hendry et al., 2008; Merilä and Hendry, 2014; Beaman et al., 2016). For instance, thermal plasticity enable fish to rapidly adjust their metabolism to environmental temperature (Narum et al., 2013). Transgenerational plasticity through parental effects is also an important evolutionary mechanism, because it can directly translate the effects of parental stress environment on offspring phenotype (Mousseau, 1998). However, parental effects can have negative or positive effects on offspring fitness.

On one hand, negative parental effects are expected for instance if there is a mismatch between parental and offspring environmental conditions, which is the case in stochastic environments (Bateson et al., 2014). In addition, intrinsic costs of plasticity and stress response can also reduce offspring fitness (Ghalambor et al., 2007; Räsänen and Kruuk, 2007). For instance, descendants of cortisol-treated females have a lower tolerance to thermal stress in Atlantic salmon (Eriksen et al., 2006, 2007), and stressed parents of Atlantic cod *Gadus morhua* sire offspring with malformations and decreased survival (Morgan et al., 1999). Toxic stressors can also trigger the induction of genes coding for oxidative and cellular stress across generations in zebrafish (Armant et al., 2017). In addition, DNA alterations resulting from oxidative stress in parental gonadic cells decrease the quality of gametes and offspring (Devaux et al., 2015; Herráez et al., 2017). In these cases, negative maladaptative effects of transgenerational stress are expected on offspring fitness.

On the other hand, some parental effects can be beneficial for offspring fitness, if they preadapt the young to the same conditions

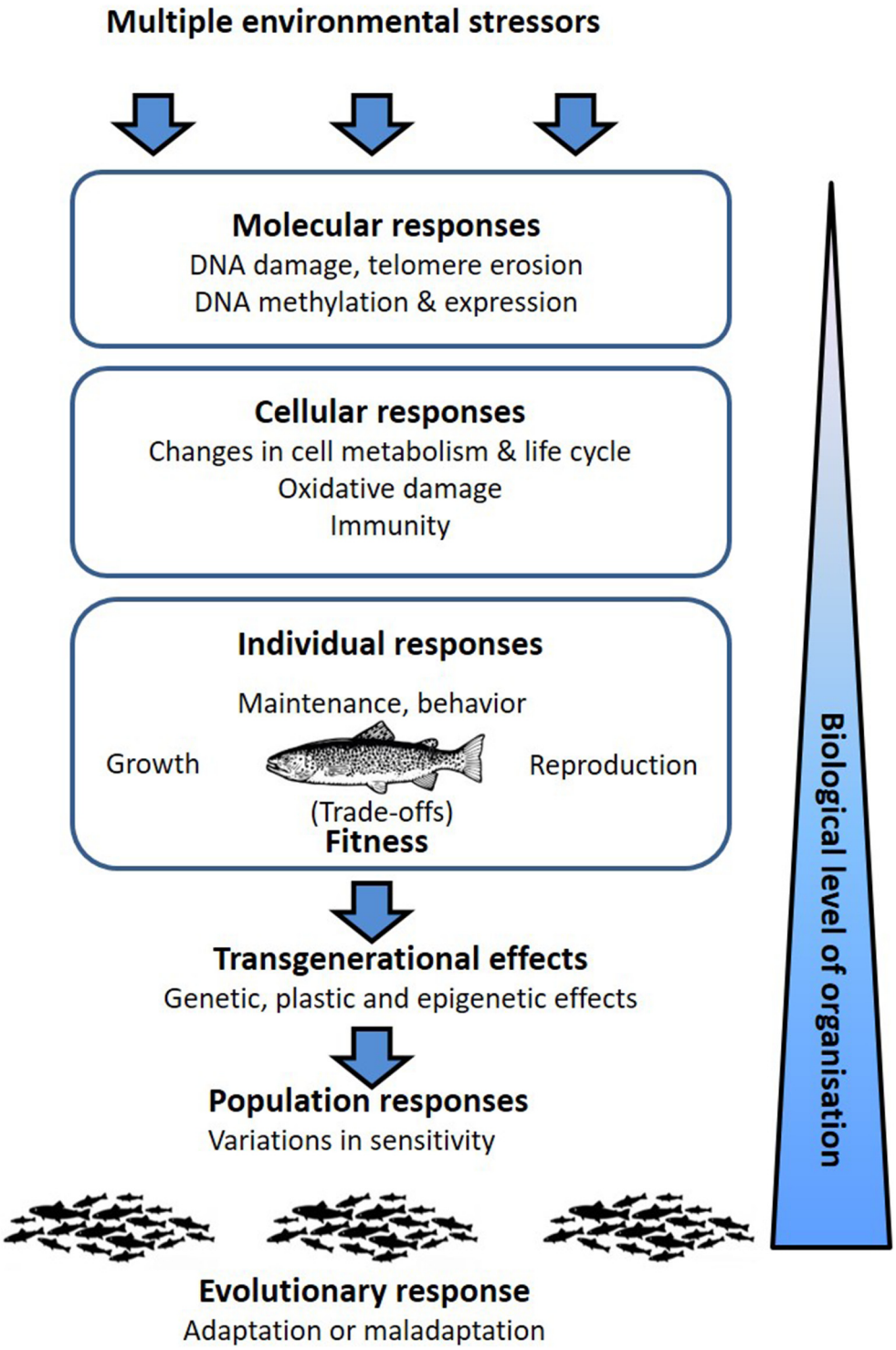

Fig. 2. Fish stress responses across levels of biological organization, from molecules to populations.

encountered by parents (Mousseau, 1998). For instance, parents of three-spined sticklebacks *Gasterosteus aculeatus* exposed to parasites can improve offspring response to the same parasites later on (Kaufmann et al., 2014). Sheepshead minnows *Cyprinodon variegatus* adaptively program their offspring growth to the temperature they will experience, which improves their growth and survival (Salinas and Munch, 2012). However, there is often a trade-off between positive and negative effects generated by trans-generational stress effects. For instance, positive trans-generational effects of UV radiation on offspring survival are associated with increased costs on molecular damage and infection rate in guppies (Ghanizadeh Kazerouni et al., 2017). These examples suggest that transgenerational effects of stressors are more important than previously thought, but that their associated costs can cause adaptive or maladaptive plasticity depending on conditions and underpinning mechanisms.

Recent studies have unveiled some mechanisms underpinning transgenerational effects of stressors and have highlighted the crucial role of epigenetics in adaptive processes (Beldade et al., 2011; Rey et al., 2016; Danchin et al., 2019). Epigenetic changes in DNA in response to stressors (such as changes in methylation and expression

levels) are more frequent than previously thought, although their functional effects are not always clearly characterized (Nikinmaa and Rytkönen, 2011). Stress exposure can cause strong epigenetic changes in some genes of parents that are transmitted to their eggs and embryos (Feil and Fraga, 2012; Mirbahai and Chipman, 2014; Pierron et al., 2014; Vandegehuchte and Janssen, 2014; Cavalieri and Spinelli, 2017). For instance, stress induce epigenetic changes in genes regulating defense and metabolism pathways, cell formation and development, bones and muscles formation, as well as neurologic development (e.g. Mirbahai and Chipman, 2014; Vandegehuchte and Janssen, 2014). Interestingly, these epigenetic changes are transmitted to offspring, and thus impact the evolutionary trajectory of populations. For instance, offspring of stressed sticklebacks *Gasterosteus aculeatus* have divergent brain transcriptomes and different levels of expression of DNA methylases, which is likely affecting their behavior and fitness across generations (Metzger and Schulte, 2016, 2017). These studies suggest that transgenerational stress effects and stress tolerance depend partly on epigenetic effects, and that adaptation (or maladaptation) to environmental stressors might well be faster than previously thought (Fig. 2). Under global changes, the pace of environmental changes likely exceeds the rate of genetic evolutionary changes, so that such rapid plastic and epigenetic responses to environmental stressors might be crucial and result in local adaptation depending on the rate of environmental changes (Hendry et al., 2008; Crozier and Hutchings, 2014; Rey et al., 2016; Danchin et al., 2019). However, more studies are needed to characterize the resulting effects on population adaptation and persistence.

In addition, determining which evolutionary mechanisms are responsible for population divergence is still a challenge, because a combination of all selective processes is likely to occur. For instance, adaptive plasticity depends on genetic variations, and there is often a selection for different levels of plasticity, which complicates the evolutionary trajectories of fish evolving in stressful environments (Kawecki and Ebert, 2004; Ghalambor et al., 2007; Bateson et al., 2014; Beaman et al., 2016). Consequences for population persistence will also strongly depend on standing intraspecific variations in existing populations and gene flow, and on spatio-temporal scale of environmental perturbations (Fitzpatrick and Reid, n.d.; Ghalambor et al., 2007; Merilä and Hendry, 2014; Hendry, 2016; Hamilton et al., 2017; Hendry et al., 2017; Whitehead et al., 2017). One of the challenges for future studies will be to take into account these spatio-temporal scales of variations, and to integrate the effects of multiple stressors to better predict the effects of human activities on the evolutionary trajectories of wild fish populations.

6. Conclusion

To conclude, existing studies highlight the need to use multiple stress approaches across biological scales to better understand the effects of human-driven perturbations on fish populations. Recent literature highlights the central role of metabolism in the stress response of fish from molecules to the whole individual. Depending on the duration, level and combination of stressors, fish can set up different metabolic strategies and energy allocation patterns, which could explain the high variability in deleterious effects on fish fitness and population persistence. Importantly, some of these effects are transmitted across generations with potential impacts on the evolutionary trajectories of wild populations. With this review, we hope to encourage future studies to bridge the gap between molecular and evolutionary approaches to better predict the impacts of present and future stressors on aquatic wildlife under global changes.

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