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REVIEW

Bioenergetics in environmental adaptation and stress tolerance of aquatic ectotherms: linking physiology and ecology in a multi-stressor landscape

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ABSTRACT

Energy metabolism (encompassing energy assimilation, conversion and utilization) plays a central role in all life processes and serves as a link between the organismal physiology, behavior and ecology. Metabolic rates define the physiological and life-history performance of an organism, have direct implications for Darwinian fitness, and affect ecologically relevant traits such as the trophic relationships, productivity and ecosystem engineering functions. Natural environmental variability and anthropogenic changes expose aquatic ectotherms to multiple stressors that can strongly affect their energy metabolism and thereby modify the energy fluxes within an organism and in the ecosystem. This Review focuses on the role of bioenergetic disturbances and metabolic adjustments in responses to multiple stressors (especially the general cellular stress response), provides examples of the effects of multiple stressors on energy intake, assimilation, conversion and expenditure, and discusses the conceptual and quantitative approaches to identify and mechanistically explain the energy trade-offs in multiple stressor scenarios, and link the cellular and organismal bioenergetics with fitness, productivity and/or ecological functions of aquatic ectotherms.

KEY WORDS: Aerobic scope, Basal maintenance, Energy metabolism, Energy trade-off, Stress tolerance

Introduction

Organisms are open systems that depend on external energy to create and maintain body structures and perform work. Organisms can store energy in the form of energy-rich chemical compounds or ion gradients, and release energy in the process of work and, eventually, during decomposition of the accrued biomass. Bioenergetics can thus be defined as a sum of all processes within a living system that transform external energy sources into the biologically useful chemical, mechanical and transport work (Skulachev et al., 2013). Energy fluxes are fundamental for all biological processes and have direct implications for the organism's fitness that increases as a function of net energy flux (Chen and Nielsen, 2019; Pyke, 1984; Spotila and Standora, 1985). Furthermore, energy transformations within an organism serve as a focal point for the energy fluxes that shape ecosystems through the organism–environment and organism–organism (e.g. trophic web) interactions, making bioenergetics an important functional trait that directly links organismal physiology with ecological and ecosystem processes.

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Energy is not only a fundamentally important commodity, but also a fundamentally limited one for organisms. In nature, the amount of food available to an organism is finite, and feeding *ad libitum* does not typically occur outside the laboratory or captivity settings. Furthermore, the capacity of the physiological and cellular systems to assimilate the ingested energy is inherently limited (Fig. 1A). For example, plants assimilate only ∼1–2% of the solar energy that reaches the Earth's surface, and animals assimilate on average ∼10% (ranging from ∼1–5% in endotherms to ∼5–15% in ectotherms) of the energy from the consumed biomass. In animals, energy assimilation is constrained by the volume and surface area of the digestive compartment as well as the activity of the digestive enzymes and absorptive epithelia (Karasov and Douglas, 2013). Furthermore, digestion and assimilation of chemical energy from food is energetically costly, as demonstrated by the specific dynamic action (SDA), a strong increase in the metabolic rate of an organism following a meal (McCue, 2006). Despite some functional and morphological plasticity of the digestive compartment, the energy assimilation system of an animal is tuned to the prevailing food conditions of its habitat with very modest excess capacity (Karasov and Douglas, 2013).

The second bottleneck in energy fluxes is set by the capacity of the catabolic systems to convert assimilated energy into the form that can be used for biologically useful work (Fig. 1A). The main universal energy currency of an organism is adenosine triphosphate (ATP) and other high energy phosphates that can be easily converted into ATP such as guanosine triphosphate (GTP), phosphocreatine or phosphoarginine. Over 90% of ATP of aerobic organisms (including most animals) is generated by mitochondria through a coupled process of organic substrate oxidation, electron transport and ATP synthesis called oxidative phosphorylation (OXPHOS). Mitochondria convert the chemical energy contained in organic compounds into the potential energy of an electrochemical gradient across the inner mitochondrial membrane (called the protonmotive force, Δp) which is then used by the mitochondrial F_0–F_1-ATPase to generate ATP. The protonmotive force is created by the mitochondrial electron transport system (ETS) that uses energy of the redox reactions in a series of electron carriers to pump the protons from the mitochondrial matrix to create Δp. In ectotherms, the ETS capacity is a limiting factor for ATP synthesis, controlling >80–90% of the OXPHOS flux (Chamberlin, 2004a,b; Ivanina et al., 2016; Kurochkin et al., 2008; Kurochkin et al., 2011).

The delivery of oxygen and nutrients to the cells is also subject to the constraints of the respiratory and circulatory systems (Darveau et al., 2002; Hochachka et al., 2003; West et al., 2002). This limitation becomes apparent under conditions of high energy demand such as during intensive exercise (Darveau et al., 2002; Hochachka et al., 2003). In aquatic ectotherms, the capacity of the oxygen and nutrient delivery might also become limiting during

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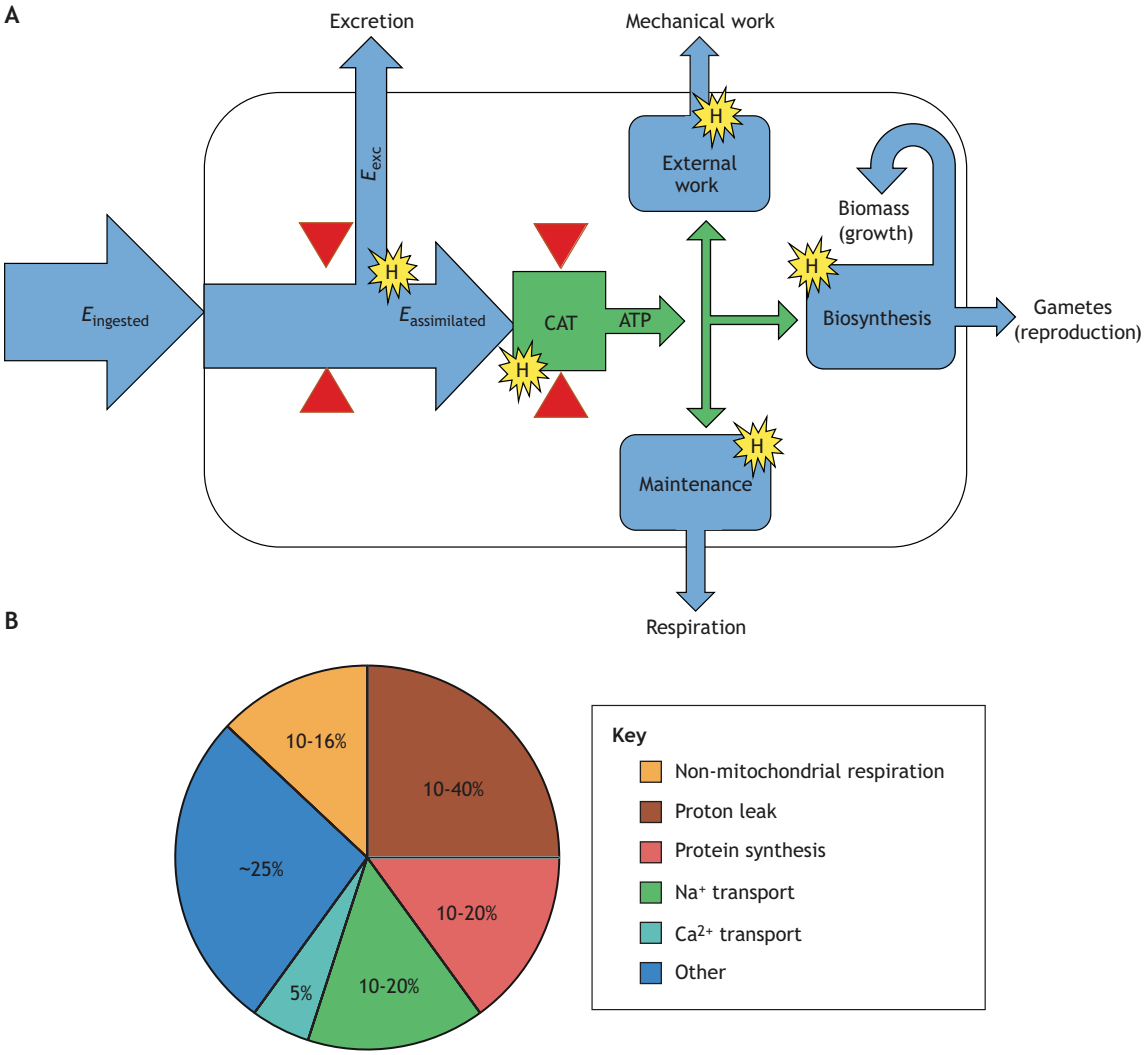

Fig. 1. A schematic representation of the energy budget of an animal. (A) Energy (in the form of chemical energy of organic compounds) is ingested by an organism ($E_{ingested}$), and a fraction of it is assimilated by the digestive epithelia ($E_{assimilated}$) while some is lost with excreta (E_{exc}). For $E_{assimilated}$ to become usable by an organism, it must be converted into the chemical form of ATP through catabolism (CAT). The generated ATP is then invested in maintenance, biosynthesis or external work. Maintenance encompasses all costs involved in the maintenance of cellular and organismal homeostasis. Energy invested in biosynthesis is partially deposited as biomass and partially released in the form of gametes during reproduction. Energy invested in mechanical work may be used for locomotion, prey capture, defense, modification of the environment (e.g. digging, nest building) and other types of activities. Due to the inherent inefficiencies of energy conversions, some energy is lost as heat (shown by 'H') at every step of the energy cascade. Red triangles indicate intrinsic constraints of the energy assimilation and conversion (catabolism) capacity. (B) Cellular energy costs measured as the fractional rate of oxygen consumption under basal conditions in typical ectotherm cells.

warming, reflecting a concomitant rise in the tissue oxygen demand (due to the Q_{10} effects on metabolism) and temperature-driven decline in oxygen solubility in water (Bozinovic and Pörtner, 2015; Deutsch et al., 2015; Pörtner et al., 2017). Thus, oxygen delivery might present an additional bottleneck for energy flux in the organism, especially when the metabolic rates are close to the maximum and/or the ambient oxygen levels decline.

Due to the extrinsic and intrinsic constraints on energy flux, the amount of energy available to an organism at any given time is restricted and must be allocated to different fitness-related activities such as production (including somatic growth and reproduction), maintenance and activity (including mechanical work involved in a variety of animal behaviors) (Fig. 1A). Balancing energy allocations under conditions of the energetic constraints can result in trade-offs between different energy-demanding functions. For example, trade-offs between the dispersal behavior (involving energetically costly flight) and reproduction have been recorded in insects (Langellotto et al., 2000; Tanaka and Suzuki, 1998). Energetic trade-offs are commonly observed between reproduction and maintenance, as shown by negative correlations between reproductive investment and female longevity in insects (Attisano et al., 2012; Blacher et al., 2017; Tanaka and Suzuki, 1998), and between reproductive investment and immunity in endotherms (Carlton et al., 2014; Demas and Sakaria, 2005; French et al., 2011) and ectotherms (Ahtiainen et al., 2005; Lourenco et al., 2009; Schwenke et al., 2016). The patterns of energy allocation to different energy-demanding functions are plastic depending on the life cycle stage and the environmental context (Carlton et al., 2014; Maklakov and Chapman, 2019; Skibiel et al., 2013). Nevertheless, the common occurrence of energetic trade-offs in animal life histories underscores the importance of bioenergetic considerations in understanding animal performance, plasticity and adaptations to the challenges posed by their environments.

Here I provide an overview of the energy-dependent physiological and cellular mechanisms of stress response and protection, assess their role for energy homeostasis and organismal fitness in the context of multiple stress exposures, and discuss the potential approaches to quantify the multiple stressor impacts based on bioenergetics markers and modeling. I focus on aquatic ectotherms due to a long tradition of using bioenergetics- and production-based approaches in these organisms that provide the theoretical framework for the bioenergetic underpinnings of environmental stress tolerance, as well as examples of successful application of bioenergetics to assess the physiological impacts and ecological outcomes of multiple stressor scenarios. However, the fundamental principles discussed in this Review are applicable to all animal heterotrophs.

Energy metabolism at the hub of stress effects and tolerance

Stress can be defined as the exposure of an organism to an abiotic or biotic forcing factor (a stressor) that results in a shift of one or more biological processes from their respective homeostatic set points (Kültz, 2020). Exposures to stressors have direct implications for energy balance as the stress-induced disruption of homeostasis must be corrected to ensure the organism's survival. Reinstatement of homeostasis requires energy to accomplish coordinated changes in the cellular, physiological, morphological and/or behavioral phenotypes to achieve the physiological steady state, protect from the stress-induced damage, and minimize a decrease in the organism's performance and fitness. The entirety of these compensatory and protective changes comprise the stress response of an organism.

The homeostasis maintenance is the main contributor to the basal maintenance costs of an organism. In endotherms, the energy costs of basal maintenance are commonly assessed as the basal metabolic rate (BMR), defined as the minimum metabolic rate of a normothermic resting organism in the absence of digestive, circadian or other increments in metabolic heat production and within the organism's thermoneutral zone (Swanson et al., 2017). In ectotherms, the standard metabolic rate (SMR) is used as a surrogate for the BMR and is defined as the minimum metabolic rate of a resting organism in the post-absorptive state (Priede, 1985). The energy costs of the basal maintenance reflected in the BMR or SMR represent the minimum energy input required for organismal survival. In animal cells, about 90% of the oxygen is consumed by mitochondria, with the rest utilized by non-mitochondrial oxidoreductases (Brand et al., 1991; Cherkasov et al., 2006; Hulbert and Else, 2000; Hulbert et al., 2002; Rolfe and Brown, 1997). Of the mitochondrial oxygen consumption, ∼20–40% is uncoupled respiration (constituting the so-called proton leak) and ∼60–80% is used to sustain cellular ATP turnover (Brand et al., 1991; Cherkasov et al., 2006; Hulbert and Else, 2000; Hulbert et al., 2002; Rolfe and Brown, 1997). A large fraction of the ATP turnover is used to maintain the homeostatic *status quo* of the cell, in particular the protein homeostasis and ion gradients across the cellular and organelle membranes (Fig. 1B). These biological processes are sensitive to environmental stressors, and increased energy investments in these cellular activities represent a proximate cause for stress-induced elevation in the SMR and trade-offs with other fitness functions.

Proteome synthesis and maintenance

The maintenance of protein homeostasis involves *de novo* synthesis of proteins to maintain cellular structure and function, activity of the chaperone systems that uphold integrity of existing proteins, and protein breakdown to remove damaged or aged proteins. All these processes are ATP or GTP dependent; however, due to experimental limitations, the energy costs of protein synthesis are the best studied. Protein synthesis costs comprise ∼10–20% of oxygen consumption (∼15–40% of ATP turnover) in adult ectotherms (Brand et al., 1991; Cherkasov et al., 2006; Fuery et al., 1998; Hulbert and Else, 1999; Hulbert et al., 2002). However, in some cell types (such as immortalized cell lines and macrophages of fish), as well as in invertebrate embryos and larvae, protein synthesis costs can make up ∼50–75% of cellular oxygen consumption (Frieder et al., 2017; Pace and Manahan, 2006; Pan et al., 2015; Smith and Houlihan, 1995). These values are based on the experimental inhibition of protein translation and thus represent low estimates that do not account for the energy costs of transcription, alternative splicing, protein processing and post-translational modifications (Conaway and Conaway, 1988; Depaoli et al., 2019). The energetic burden of proteome maintenance might be close to the cellular limit so that surplus protein production carries direct and significant fitness costs as shown in bacteria (Dong et al., 1995) and yeast (Farkas et al., 2018; Kafri et al., 2016). Even a modest increase in the protein burden can have catastrophic consequences, as shown for *E. coli*, where the proteosynthetic machinery collapses and growth ceases when excess protein production reaches 30% of the total proteome (Dong et al., 1995).

Molecular chaperones (in particular, the heat shock proteins, HSPs) play a key role in cellular protein homeostasis. Some HSPs (including several isoforms of HSP70, HSP100 and HSP60) are constitutively expressed and participate in folding and maturation of newly synthesized proteins, whereas others are induced by exposure to stressors such as temperature, osmotic stress, ultraviolet (UV) light, toxic agents or radiation (Feder and Hofmann, 1999; Sørensen et al., 2003). The induction of the HSPs by heat and other stressors was first described in the 1960s by Ferruccio Ritossa in his pioneering work on *Drosophila* (Ritossa, 1962, 1996), and has since been recognized as a universal cellular response to any stressor that results in protein damage (Feder and Hofmann, 1999; Sørensen et al., 2003). HSPs are highly abundant, constituting up to 10–15% of cellular proteins by mass (Finka and Goloubinoff, 2013; Neidhardt et al., 1984), and this fraction can increase during stress exposures, often at the expense of important housekeeping proteins (Finka et al., 2015). Many HSPs (including HSP70, HSP100 and HSP40) require ATP for their function (Nguyen et al., 2019; Sharma et al., 2010), so that expression and function of HSPs presents a significant energy cost of proteome maintenance above and beyond the costs of protein synthesis. To date, there are no studies that directly assess the contribution of the chaperone function of HSPs to cellular ATP turnover, and this important aspect of the cellular energy budget awaits innovative experimental approaches for further investigation.

Recent studies in model organisms (including mammals and yeast) show that protein breakdown is a major ATP sink in the cell. Damaged proteins are targeted to the 26S proteasome through the ATP-dependent addition of a ubiquitin chain, and further degraded in an ATP-dependent manner (Peth et al., 2013, 2010). The ATP costs of proteasomal degradation can be considerable depending on the size of the protein. For example, the breakdown of dihydrofolate reductase (a small protein of ∼25 kDa) requires hydrolysis of 50–160 ATP molecules at a rate of ∼230–370 ATP molecules min^{-1} (Peth et al., 2013). Mitochondrial ATP-dependent (AAA) proteases (such as Lon and ClpXP) that remove oxidatively damaged mitochondrial proteins (Glynn, 2017; Koppen and Langer, 2007; Smakowska et al., 2014) consume ATP at rates that might exceed that of the 26S proteasome (e.g. ∼610 ATP molecules min^{-1} for ClpXP) (Kenniston et al., 2003). Furthermore, even though

lysosomal proteases do not directly use ATP, they depend on the highly acidic lysosomal environment maintained by the active proton pumping (Gronostajski et al., 1985). Given a constant turnover of cellular proteins (with most cellular proteins having a half-life less than 24 h) (Chen et al., 2016; Toyama and Hetzer, 2013), protein breakdown can strongly contribute to basal maintenance costs.

Stress-induced protein damage can result in elevated protein degradation and *de novo* biosynthesis to replace the damaged proteins. Furthermore, stress exposures can selectively upregulate stress protection systems such as molecular chaperones (including HSPs), anti-oxidant enzymes, scavengers of free radicals and toxic agents, and cellular quality control mechanisms (such as autophagy and mitophagy). Stress-induced systemic responses (such as inflammation or the immune response) also carry a significant energy cost due to immune cell proliferation, production of immune and inflammation-related molecules, and cytokine-induced elevation of energy expenditure (Ganeshan et al., 2019; Lacourt et al., 2018; Wang et al., 2019; Wang and Ye, 2015). An increase in protein synthesis and/or turnover is a common response to a broad range of environmental stressors such as extreme temperatures, salinity stress, ocean acidification, and pro-oxidant and toxicant exposures (Cherkasov et al., 2006; Frieder et al., 2017; Gedamu et al., 1983; Goering et al., 1993; Hawkins and Hilbish, 2009; Ivanina et al., 2008; Iwama et al., 1999; Kassahn et al., 2009; Pan et al., 2015; Suresh et al., 1983). A notable exception from this pattern are genotoxic stressors (such as UV irradiation) that inhibit transcription (and thus protein synthesis) due to direct damage to DNA (Kantor and Hull, 1979; Straaten et al., 1992). Thus, upregulation of protein turnover might be considered a sensitive marker of cellular stress as well as an ATP sink contributing to elevated maintenance costs in stress-exposed organisms. Further studies are required to dissect the bioenergetics consequences of stress-induced proteome maintenance by separately assessing the contributions of *de novo* protein synthesis, protein breakdown and activity of the molecular chaperones, and ideally, measuring the costs of individual protective systems such as anti-oxidant defense, detoxification or autophagy.

Ion and acid–base homeostasis

Ion and acid–base regulation constitutes another major cellular energy sink because of the ATP requirements of membrane ion pumps (most notably, Na^+–K^+-ATPase, H^+-ATPase and Ca^{2+}-ATPase) and dependence of other transport mechanisms on the ion gradients created by these pumps (Claiborne et al., 2002; Larsen et al., 2014). Na^+–K^+-ATPase (NKA) is a major ATP consumer, accounting for 10–20% of cellular metabolism (Fig. 1B) (Geisler et al., 2017; Heerlein et al., 2005; Pan et al., 2015; Silver and Erecińska, 1997). Abiotic stressors that alter intracellular ion concentrations and/or the ion gradients between the extracellular and intracellular milieu result in elevated ATP consumption driven by an increase in NKA activity. Thus, NKA activity is commonly modulated by osmotic stress (Huang et al., 2010; Jia and Liu, 2018) with a stronger response found in osmoregulators than osmoconformers (Ivanina et al., 2020; Whiteley et al., 2018). Abiotic stressors such as elevated temperature (Nattie, 1990), ocean acidification (Melzner et al., 2020) or hypoxia (Grieshaber et al., 1994; Pörtner et al., 1984) can disrupt acid–base homeostasis and incur additional energy costs for the ion transport processes. Compensatory increases in ion and acid–base transport activities were proposed as an underlying mechanism of elevated energy costs of biomineralization in marine calcifiers under ocean acidification scenarios (Clark, 2020; Frieder et al., 2017; Pan et al., 2015; Stumpp et al., 2012; Wood et al., 2010, 2008). Elevated CO_2 and low pH can also increase energy allocation to the NKA, as shown in echinoderm larvae (Frieder et al., 2017), mantle tissues of marine bivalves (Ivanina et al., 2020) and fish gills (Deigweiher et al., 2010). Contributions of other ion transport mechanisms (other than NKA activity) have not been extensively studied in aquatic ectotherms (Ivanina et al., 2020) and require further investigation.

Mitochondrial proton leak

Mitochondrial proton leak reflects the baseline activity of the mitochondrial ETS system needed to counteract all futile proton and cation cycles (not coupled to the ATP production) and prevent depolarization of mitochondria (Rofle and Brand, 1997). Basal proton leak is in part (~5%) due to the proton conductance of the lipid bilayer but mostly reflects the proton translocation by the substrate and adenylate transporters in the inner mitochondrial membrane (Brand et al., 2005; Divakaruni and Brand, 2011; Nanayakkara et al., 2019). This futile proton cycling constitutes a tremendous energetic cost (20–40% of the BMR and SMR) for animal cells (Fig. 1B). However, it also plays important physiological functions, allowing for the flexibility of energy metabolism in response to changes in cellular ATP demand, maintaining carbon flux when ATP demand is low, and preventing excessive reactive oxygen species (ROS) production (Divakaruni and Brand, 2011).

Exposure to stressors can elevate the rate of the mitochondrial proton leak (Cherkasov et al., 2007; Divakaruni and Brand, 2011; Mendez-Romero et al., 2020), thereby raising the energy cost of mitochondrial maintenance. This change may be an indirect consequence of stress-induced changes in ETS activity (driven by energy demand) and/or reflect a change in the proton conductivity (leakiness) of the inner mitochondrial membrane. Thus, exposure to elevated (supraoptimal) temperatures almost universally increases the leakiness of mitochondrial membranes in vertebrate and invertebrate ectotherms (Cherkasov et al., 2006, 2010; Iftikar and Hickey, 2013; Kamunde et al., 2019; Leo et al., 2017; Mueller et al., 2011; Oellermann et al., 2020; Onukwufor et al., 2015, 2016; Sappal et al., 2014). Similar effects of elevated temperature on mitochondrial proton leak are found in endotherms (Jarmuszkiewicz et al., 2015; Mitov et al., 2017), suggesting that this mitochondrial phenotype might be conserved in metazoans. Elevated mitochondrial proton leak is also involved in the early metabolic response to salinity change, returning to baseline when the new osmotic steady state is reached (Brijs et al., 2017; Haider et al., 2018; Sokolov and Sokolova, 2019). Exposure to toxic metals (such as cadmium, copper or zinc) leads to an increase in the proton conductivity of the inner mitochondrial membrane and progressive loss of mitochondrial efficiency and coupling (Braz-Mota et al., 2018; Ivanina et al., 2012; Kurochkin et al., 2011; Onukwufor et al., 2015; Sappal et al., 2014; Sokolova, 2004). Contaminants of emerging concern (CECs) such as pharmaceuticals and personal care products can also stimulate proton leak in mitochondria of aquatic ectotherms (as shown in Chinook salmon; Yeh et al., 2017); however, due to the great diversity of the involved CECs, the cause–effect links to a certain compound are yet to be established.

The stress-induced elevation of mitochondrial proton leak represents a double whammy from the viewpoint of cellular energetics, as the demand for oxygen and nutrients to counteract the proton leak increases while the efficiency of the mitochondrial ATP synthesis declines. While elevated mitochondrial proton leak in response to abiotic stressors is well documented, the molecular mechanisms underlying this effect are not yet fully understood. Among these mechanisms, the role of uncoupling proteins (UCPs)

and membrane lipids in the stress-induced increase in proton conductance represent fruitful avenues for further research. Thus, acclimation to sub- or supraoptimal temperature, salinity or elevated CO_2 levels can affect the membrane composition of ectotherm mitochondria shifting the concentrations of cardiolipin, sterols and the degree of the fatty acid saturation (Fiorini et al., 2019; Long et al., 2019; Strobel et al., 2013), and altering the lipid–protein interactions (Fiorini et al., 2019). Further studies are needed to examine the implications of these changes for mitochondrial proton leak and the associated energy costs of mitochondrial homeostasis.

Detoxification mechanisms

Exposure to natural toxins and anthropogenic pollutants disturbs the cellular homeostasis due to direct interactions of toxicants and their metabolites with proteins, DNA or lipids, as well as the secondary stress due to the generation of ROS. The recovery of cellular homeostasis involves activation of elimination mechanisms (to facilitate the efflux of toxicants from the cell), detoxification of accumulated compounds, and repair or replacement of macromolecules damaged by the toxicants, their metabolites or ROS. These cellular detoxification and stress defense mechanisms are ATP dependent and their activation might result in considerable energy costs.

Inorganic pollutants such as trace metals exert toxicity by binding to DNA or proteins, which results in a loss of structural integrity and impaired activity of the macromolecules (Zalups and Koropatnick, 2010), and can lead to oxidative stress due to Fenton-type reactions (Stohs and Bagchi, 1995; Valko et al., 2005) or impaired mitochondrial respiration (Cherkasov et al., 2007; Kurochkin et al., 2011; Sokolova, 2004). Detoxification of trace metals involves binding to thiol-containing ligands such as metallothioneins and glutathione, which decreases the intracellular concentrations of the most toxic (ionic) form of the metal (Zalups and Koropatnick, 2010), whereas the metal-induced redox misbalance and protein damage are dealt with by cellular anti-oxidant systems and protein chaperones (e.g. HSPs) (Haap et al., 2016; Ivanina et al., 2008; Jomova and Valko, 2011; Micovic et al., 2009; Monserrat et al., 2007; Valko et al., 2005; Yu et al., 2006). The metal detoxification mechanisms (except the HSPs) do not directly consume ATP; however, elevated expression of metallothioneins and HSPs incurs energy costs for protein biosynthesis and might lead to trade-offs between different cellular protective systems (Haap et al., 2016; Ivanina et al., 2008; Saydam et al., 2003).

The membrane ATP-binding cassette (ABC) transporters constitute the first line of defense against organic pollutants (including natural toxins and man-made xenobiotics). While many ABC transporters transfer endogenous substrates such as lipids, sterols and peptides, several members of the family [including P-glycoproteins (P-gPs) and multidrug-resistance-associated proteins (MRPs 1–5)] play an important role in the efflux of organic pollutants and their metabolites (Ferreira et al., 2014; Volf, 2018). The ABC transporters also contribute to elimination of toxic metals such as cadmium conjugated with glutathione (GSH) (Borst et al., 2000; Huynh-Delerme et al., 2005; Ivanina and Sokolova, 2008). Translocation of one molecule of the substrate by the ABC transporters typically requires hydrolysis of two ATP molecules (Rees et al., 2009).

In the cell, organic xenobiotics undergo biotransformation through the coupled oxidation–reduction (Phase I) and conjugation (Phase II) reactions (Omiecinski et al., 2010). The Phase I biotransformation is catalysed by several enzyme systems, most notably the family of cytochrome P450 (CYP450) monooxygenases (Omiecinski et al., 2010). ROS are often formed as a by-product of Phase I biotransformation and can amplify the toxicity of xenobiotics (Hrycay and Bandiera, 2015). Phase II of biotransformation involves conjugation of the parent compound or its metabolites to an organic substrate (e.g. glutathione or amino acid), or a side group modification such as glucuronidation, sulfation or methylation that increases hydrophilicity of the compound and aids in its excretion (Omiecinski et al., 2010). Phase I and II biotransformation reactions are not directly ATP consuming (Omiecinski et al., 2010), and the energy costs associated with the activation of these systems are mostly due to the production of inducible biotransformation enzymes (such as CYP450) and anti-oxidants.

To date, there have been few attempts to quantify the energy costs of detoxification in pollutant-exposed aquatic organisms. In the oyster *Crassostrea virginica*, exposure to a toxic metal (cadmium) for 20–40 days led to a considerable increase in the basal maintenance costs by ∼30–100% (depending on the temperature) (Cherkasov et al., 2006; Ivanina and Sokolova, 2008; Lannig et al., 2006a,b). This increase was traceable from the whole organism (Lannig et al., 2006a,b) to the tissue (Ivanina and Sokolova, 2008) and cellular levels (Cherkasov et al., 2006), and reflected the increased investment into *de novo* protein synthesis and elevated mitochondrial proton leak (Cherkasov et al., 2006). Similarly, elevated ATP demand (shown by higher steady-state ATP levels and enhanced breakdown of glycogen reserves) was found in cadmium-exposed crabs (*Sinopotamon henanense*) and was associated with elevated synthesis of protective proteins (such as metallothioneins) (Yang et al., 2015). Activation of detoxification mechanisms by exposure to organic xenobiotics has been reported to add ∼5–10% of the basal metabolic costs in animals (Castañeda et al., 2009; Ivanina and Sokolova, 2008). The cumulative lifetime costs of detoxification can be high, causing trade-offs between toxicant tolerance and fitness traits (such as growth, reproduction or development) in animals and plants (Diniz et al., 2015; Erasmus et al., 2019; Kliot and Ghanim, 2012; Mireji et al., 2010; Wilson, 1988). High fitness costs of detoxification are also shown by a rapid loss of tolerance after the selective pressure of the toxicant is removed (Levinton et al., 2003; Maestri et al., 2010; Mireji et al., 2010).

Molecular evidence for the role of bioenergetics in the stress response

Advancement of large-scale molecular techniques (such as transcriptomics and proteomics) provides an integrated, system-level view of cellular shifts in response to stressors and emphasizes the crucial importance of bioenergetics in stress responses (Evans, 2015; Kültz, 2003, 2005; Tomanek, 2011; Ungaro et al., 2017). The pathways involved in energy metabolism and proteome maintenance commonly appear as the top hits among the pathways differentially regulated by exposures to various stressors. The relative importance of these pathways depends on species physiology and the severity of the stressor. Thus, moderate warming (in the supraoptimal yet sublethal temperature range) upregulated genes involved in glucose metabolism and lipid mobilization in the king scallop *Pecten maximus* at the expense of other cellular processes such as DNA repair (Artigaud et al., 2015). Upregulation of the lipid transport and aerobic energy metabolism pathways during moderate warming (22 versus 18°C) was also found in a temperate ascidia, *Ciona intestinalis* (Lopez et al., 2017). In Antarctic benthic invertebrates, the transcripts encoding mitochondrial ETS were upregulated during sublethal warming in a snail (*Marseniopsis mollis*) and an echinoderm (*Cucumaria georgiana*) (characterized by low to intermediate

thermal tolerance) but not in more heat-tolerant species, including a brachiopod (*Liothyrella uva*), a crustacean (*Paraceradocus miersi*) and bivalves (*Aequiyoldia eightsii* and *Laternula elliptica*) (Clark et al., 2017). Instead, protein degradation pathways were upregulated in the more heat-tolerant Antarctic species (Clark et al., 2017). Upregulation of ATP-producing pathways including the mitochondrial ETS, citric acid cycle and anaerobic glycolysis was reported in the blue mussel *Mytilus galloprovincialis* exposed to pyrene-loaded microplastics (Avio et al., 2015), the green-lipped mussel *Perna viridis* exposed to cadmium (Leung et al., 2011) and the common carp *Cyprinus carpio* exposed to copper (Eyckmans et al., 2012). In the oyster *C. virginica*, ∼25% of differentially expressed transcripts were involved in energy metabolism and provided the best discriminators between oyster populations from forested, suburban, urban and industrialized creeks (Chapman et al., 2009). Protein synthesis and/or degradation pathways are also commonly upregulated during exposure to a variety of organic and inorganic pollutants, as shown by transcriptomics and proteomics (Dorts et al., 2014; Leung et al., 2011; Milan et al., 2016; Olsson et al., 2004; Silvestre et al., 2006; Thompson et al., 2011; Williams et al., 2008).

Unlike temperature or pollutants, the involvement of cellular ATP-producing and -consuming pathways in response to osmotic stress appears more variable and depends on the physiological osmoregulation strategy (osmoconformity or osmoregulation) of an organism, as well as the direction and degree of the salinity deviation from the species-specific osmotic optimum (Kelly et al., 2016; Tomanek, 2011). Pathways differentially regulated by osmotic stress include osmolyte metabolism (including amino acids and urea), cellular ion and water transport, molecular chaperones and pathways involved in cytoskeleton maintenance and modifications (Chen et al., 2009; Dowd et al., 2010; Evans and Somero, 2008; Ho et al., 2019; Lee et al., 2006; Muraeva et al., 2017; Su et al., 2020; Tse et al., 2014). Energy pathways (including aerobic metabolism and anaerobic glycolysis) can be stimulated (Lee et al., 2006; Muraeva et al., 2017) or suppressed by osmotic stress (Chen et al., 2009; Dowd et al., 2010; Evans and Somero, 2008; Ho et al., 2019).

An important question regarding the bioenergetics of cellular stress responses relates to the potential role of cytoskeleton remodeling in stress-induced metabolic reorganization and energy trade-offs. In ectotherms, the pathways involved in maintenance and remodeling of the cytoskeleton are commonly up- and downregulated during exposure to abiotic stressors including cold and heat stress (Artigaud et al., 2015; Fields et al., 2012; Tomanek and Zuzow, 2010; Vasquez et al., 2019; Vergauwen et al., 2010; Windisch et al., 2014), osmotic stress (Tse et al., 2014; Zhao et al., 2012), ocean acidification (Mukherjee et al., 2013; Tomanek et al., 2011) and pollutants (Campos et al., 2012; Eyckmans et al., 2012; Zapata et al., 2009). The actin cytoskeleton is the primary determinant of cell shape, attachment, movement, intracellular transport and division (Banerjee et al., 2020), and its dynamic stability and function is strictly ATP dependent (Bernstein and Bamburg, 2003; Kuiper et al., 2008; Xu and Bretscher, 2014). Recent studies indicate that cytoskeleton maintenance incurs substantial energy costs. In yeast, ATP deficiency led to a rapid loss of cytoskeleton integrity during starvation (Xu and Bretscher, 2014). In chick neurons, suppression of actin turnover reduced ATP consumption by ∼50% (Bernstein and Bamburg, 2003). Direct assessments of the relative contribution of cytoskeleton maintenance and remodeling to ATP turnover under optimum and stressful conditions are currently lacking for ectotherms, and require further investigation.

Metabolic rate depression as a strategy to survive extreme stress

Elevated energy investment into cellular protective functions depends on sufficient supply of oxygen and metabolic fuels to support high rates of ATP production. When an organism is exposed to stressors that limit oxygen or fuel supply (such as desiccation, freezing, hypoxia or starvation), such energy-extensive metabolic adjustments might become non-sustainable or counterproductive. Many stress-tolerant aquatic ectotherms have therefore evolved a metabolic avoidance strategy called metabolic rate depression (MRD) that allows time-limited survival under conditions of energy shortage (Hochachka et al., 1996; Watford, 2015). The MRD involves a coordinated decrease in ATP production and consumption that allows the metabolic rate of an organism to decrease below 5–10% of the normal SMR (Grieshaber et al., 1994; Guppy et al., 1994; Hochachka et al., 1993; Sokolova et al., 2000; Sokolova and Pörtner, 2003; Storey and Storey, 1990). In extreme cases (such as the resting life stages of some arthropods, rotifers and tardigrades), the metabolic rate during MRD is undetectable so that the organisms are classified as ametabolic (cryptobiotic) (Guppy and Withers, 1999; Jönsson and Järemo, 2003). The MRD allows the organism to conserve energy and delays the onset of homeostatic disturbances (such accumulation of metabolic wastes or collapse of the transmembrane ion gradients) incompatible with survival.

A decrease in the ATP turnover during the MRD involves suppression of all the major cellular ATP consumers including protein turnover, mitochondrial proton leak and ion transport. The mechanisms of this suppression during the MRD have been covered in several excellent reviews (Boutilier and St-Pierre, 2000; Buck and Pamenter, 2018; Hochachka et al., 1996; Ramnanan et al., 2009; Rider, 2016; Staples and Buck, 2009; Storey et al., 2011; Storey and Storey, 2004). MRD appears to be a universal and highly effective metabolic strategy to survive extreme stress conditions in animals (Guppy et al., 1994; Storey, 1998). However, although MRD can extend survival time under stress for days, weeks, or (in the case of cryptobiosis) years, it is bioenergetically unsustainable and incompatible with indefinite survival. Due to extreme energy savings, MRD curtails most essential organismal activities including locomotion, growth or reproduction. Furthermore, the delayed energy costs (due to the reinstatement of physiological homeostasis, oxidation of anaerobic end-products or replenishment of depleted energy reserves) can be substantial, as shown by a major (up to 200–500% of the BMR) overshoot of oxygen consumption rates during recovery (Ellington, 1983; Lewis et al., 2007; Maxime et al., 2000; Plambech et al., 2013; Svendsen et al., 2011; Vismann and Hagerman, 1996). The recovery costs after MRD might lead to trade-offs with other energy-demanding fitness-related functions, as shown in a stress-tolerant mammal, the naked mole rat, that enters a transient comatose state during post-hypoxic recovery, ceasing locomotion and maintaining low body temperature (Pamenter et al., 2019). Therefore, the ecological cost–benefit analysis of the role of MRD in organismal energy budget must take into account the duration, timing and recovery costs of MRD relative to important life cycle events and stages.

Energy metabolism as an integrator of multiple stress impacts

The energy dependence of life processes and the inevitable constraint of the rate at which energy can be acquired, assimilated and converted into the biologically usable form creates a basis for the trade-offs between different energy-demanding functions. Typically, basal maintenance costs have high priority in the energy allocation hierarchy because cellular and organismal homeostasis is essential

for survival as well as a necessary (albeit not sufficient) prerequisite for the organism's ability to carry out other fitness-related functions. Some exceptions occur when basal maintenance is sacrificed for the benefit of other functions such reproduction in terminal breeders (Junghanns et al., 2019; Royle et al., 2012) or activity to escape an immediate threat (Haider et al., 2018; Haider et al., 2019; Husak et al., 2016). However, such priority reversals are not sustainable and eventually lead to mortality. For the most part of an organism's life cycle, the energy costs of basal maintenance constitute a top allocation priority.

Under the conditions close to the species' optimum, selection acts to reduce the maintenance costs as much as possible under the constraints of a given environment and life style (Swanson et al., 2017). This maximizes the energy flux allocated to other fitness-related functions such as development/growth, reproduction or activity (Fig. 2). The upper ceiling to this energy flux (W_{max}) is set by the organism's capacity to assimilate energy from food and catabolize it to ATP (Darveau et al., 2002; Suarez and Darveau, 2005). The aerobic scope for performance (SFP) (defined as the energy flux available to sustain fitness-related functions after the costs of basal maintenance are covered) is thus determined by the difference between the maximum attainable metabolic flux and SMR of an organism (SFP=W_{max}–SMR, in J g^{-1} s^{-1}) (Fig. 2). Furthermore, some energy is deposited as reserve (mostly glycogen and lipids) to buffer against variation in food availability (Krams et al., 2020; Levy et al., 2012; Ratcliff and Denison, 2010).

Exposure to a broad variety of stressors activates the general cellular stress response, incurring additional energy costs for homeostasis (Fig. 2A). This results in a trade-off between survival and other fitness-related functions, as shown for cold stress tolerance and fecundity in *Drosophila* (Marshall and Sinclair, 2010), toxicity tolerance, reproduction and growth in insects and plants (Diniz et al., 2015; Kliot and Ghanim, 2012; Mireji et al., 2010; Wilson, 1988), or heat tolerance and fecundity in crustaceans (Kelly et al., 2016). Stress exposures can also lower the maximum energy flux capacity (W_{max}) due to the negative effects on catabolic processes, in particular the mitochondrial capacity and efficiency of ATP production (Ballantyne, 2004; Somero et al., 2016; Pörtner et al., 2017; Sokolova, 2018; Sokolova and Lannig, 2008; Sokolova et al., 2011; Somero et al., 2016). Furthermore, stressor exposure often decreases the amount and rate of energy assimilation (due to suppressed feeding rate and/or impaired digestive processes), as shown for elevated temperatures (Angilletta, 2001; Fontaine et al., 2018; Jutfelt et al., 2020; McConnachie and Alexander, 2004; Salin et al., 2016), hypoxia (Thomas et al., 2019), ocean acidification (Hu et al., 2017, 2018; Khan et al., 2020; Pimentel et al., 2015; Rosa et al., 2016; Stumpp et al., 2013) and pollutants (Barrera-Escorcia et al., 2010; Luo et al., 2020; Mouabad et al., 2001; Ostroumov, 2005; Rahnama et al., 2010). The net effect of multiple stressors is therefore a decrease in the aerobic SFP and the corresponding decline in the organism's fitness.

The degree of the stress-induced decrease in SFP depends on the deviation of the environmental conditions from the species-specific optimum (Fig. 2B). Moderate deviations from the optimum (the so-called pejus range) lead to a stress-induced increase in basal maintenance costs, thereby reducing SFP; yet as long as SFP remains positive over the sufficient portion of the life cycle of the organism, these conditions are compatible with long-term survival of the population. The normal habitat conditions of a species (i.e. corresponding to the center of the species' distribution range) thus encompasses the optimum and pejus conditions as seen from the bioenergetics viewpoint. As abiotic conditions further deviate from the optimum into the pessimum range, increasing energy demand for basal maintenance leads to the point where all aerobic energy flux is diverted towards homeostatic maintenance with no SFP left for growth or reproduction (Fig. 2B). In some species, the energy deficiency in the pejus range induces a hypometabolic state (the MRD) that conserves energy and extends the survival time under extreme stress conditions (Storey and Storey, 1990). In either case, SFP in the pessimum range approaches zero, and anaerobic pathways might become engaged to compensate for insufficient aerobic ATP production. This is a bioenergetically non-sustainable state where survival of an organism is possible, but the persistence of a population is not. The pessimum conditions are expected to be commonly found in the marginal populations at the periphery of the species' distribution (Sexton et al., 2009) and in the sink areas of metapopulations (Hanski, 1998), albeit the empirical studies to test this hypothesis are currently lacking.

Extreme deviations of environmental conditions from the optimum range may result in lethal stress where only short-term survival (minutes to hours) is possible (Fig. 2A). Here the combined energy fluxes of aerobic and anaerobic pathways are insufficient to support homeostasis, so that cellular damages accumulate, eventually resulting in death. It is worth noting that the SMR is not a good estimate for the energy costs of basal maintenance in the lethal range because the cellular metabolic machinery reaches the upper limit and energy debt accrues (Fig. 2B). The signs of such energy debt involve depletion of the cellular ATP stores (which are buffered under more moderate stress conditions), collapse of the essential ATP-demanding functions such as the maintenance of ion gradients across the cellular and organelle membranes and the basal protein synthesis, and elevated metabolic rate ('oxygen debt') during recovery. Short-term survival under these conditions depends on cellular protection mechanisms such as molecular chaperones (HSPs), and proteolytic and autophagic pathways that remove damaged cellular components (Flick and Kaiser, 2012; Kroemer et al., 2010; Sørensen et al., 2003). Extremely stress-tolerant organisms such as tardigrades, rotifers and some arthropods can survive environmental extremes that would be lethal to most other metazoans, but this extreme tolerance is invariably associated with cryptobiosis, which (bioenergetically speaking) moves the organism from the lethal into the pessimum range, minimizing the energy deficit (Boothby, 2019).

Focus on the bioenergetic consequences of stress exposures provides a useful platform to integrate the effects of multiple stressors that affect energy fluxes through the effects on SMR, energy assimilation or catabolism. Recent meta-analyses and modeling studies indicate that non-additive stressor interactions (Fig. 3) are common in nature (Burgess et al., 2020 preprint; Galic et al., 2018; Jackson et al., 2015; Villar-Argaiz et al., 2018). Thus, in freshwater ecosystems the net effect of multiple stressors were additive in only 16% of 286 studied responses, whereas antagonism, synergy or effect reversal by stressor combinations was found in 41, 28 and 15% of cases, respectively (Jackson et al., 2015). Similarly, in marine ecosystems the combined effects of multiple stressors on the trophic web traits (based on 320 observations) were mostly synergistic (49%) or antagonistic (47%) (Villar-Argaiz et al., 2018). Although non-additive stressor interactions are well documented (Galic et al., 2018; Holmstrup et al., 2009; Jackson et al., 2015; Villar-Argaiz et al., 2018), the mechanisms underlying these interactions are not well understood, thereby limiting our ability to predict multiple stressor outcomes in nature. One of the challenges for our understanding is finding a common metric that can measure effects of chemical, physical and biological stressors and link the

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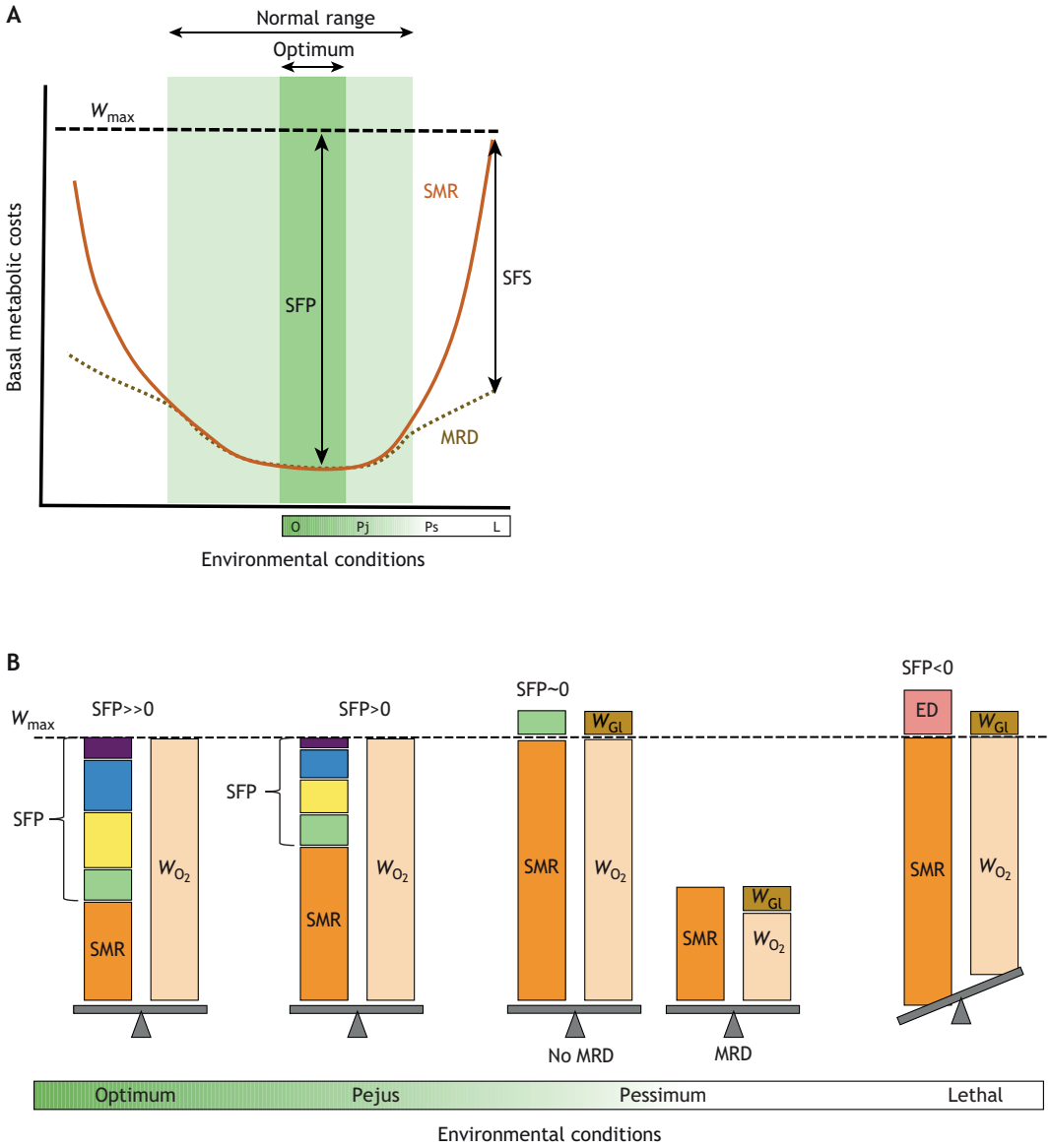

Fig. 2. Impacts of environmental stress on the energy costs of the basal maintenance and the overall energy budget of an organism. (A) Basal maintenance costs (measured as standard metabolic rate, SMR) depend on the deviation of environmental conditions from the optimum and normal ranges of the population (shown by dark green and light green shading, respectively). In some stress-tolerant species, high levels of stress can lead to a decrease of the metabolic rate below the SMR, the so-called metabolic rate depression (MRD), extending the survival time under extreme stress conditions. The difference between the normal SMR and the MRD state is defined as the scope for survival (SFS) (Hochachka, 1990). The maximum aerobic energy flux (W_{max}, in J g^{-1} s^{-1}) sets the upper limit of the sustainable metabolism of an organism, and the difference between the SMR and W_{max} defines the aerobic scope of performance (SFP). Depending on the degree of the deviation of the environmental conditions from the optimum (O), the environmental ranges are defined as pejus (Pj), pessimum (Ps) and lethal (L) (see explanations in B). (B) Environmental stress increases the costs of basal maintenance (measured as SMR) and affects energy allocation to different energy-demanding functions as well as the balance between energy demand and energy supply of an organism. Under the optimum conditions, the costs of basal maintenance (measured as SMR) are minimal, and the aerobic scope for performance (SFP) defined as the fraction of the aerobic energy flux that can be devoted to fitness-related functions such as (from the bottom to the top of the bar) locomotion/mechanical work (green), growth/biomass production (yellow), maturity/reproduction (blue), and deposition and maintenance of energy reserves (purple) is positive and maximal for the given life stage. Under these conditions, energy demand of an organism is fully covered by the aerobic ATP production (W_{O_2}). In the suboptimal and supraoptimal (pejus) range, the energy allocation to basal maintenance increases, decreasing the SFP and leading to a trade-off with other energy-demanding fitness functions. Further deviation of the conditions into the pessimum range result in a bioenergetically unsustainable state where the energy flux of the organism is fully invested into survival and the SFP available for other energy-demanding functions disappears. Low levels of essential activities (e.g. foraging) might be maintained, and the anaerobic glycolysis (W_{GL}) is engaged to compensate for insufficient aerobic ATP production. In some stress-tolerant organisms, transition into the pessimum range is associated with metabolic rate depression (MRD) to extend survival at the expense of other fitness-related functions. In the lethal range, the energy flux required to maintain cellular homeostasis is higher than the joint aerobic (W_{O_2}) and anaerobic (W_{GL}) energy flux capacity, resulting in an energy debt (ED) and accumulation of cellular damage. Note that SMR (measured as oxygen consumption) cannot serve as an estimate of organismal energy demand in the pessimum and lethal ranges due to the contributions of anaerobic metabolism to energy flux and/or accrued energy debt.

effects at different levels of biological organization. Analysis of energy budgets provides an ideal mechanistic tool to overcome this challenge, as energy investment is involved in the functional and structural responses to stressors at all levels of biological organization, from molecular interactions inside the cell to the nutrient cycles and trophic webs (Segner et al., 2014). Despite the

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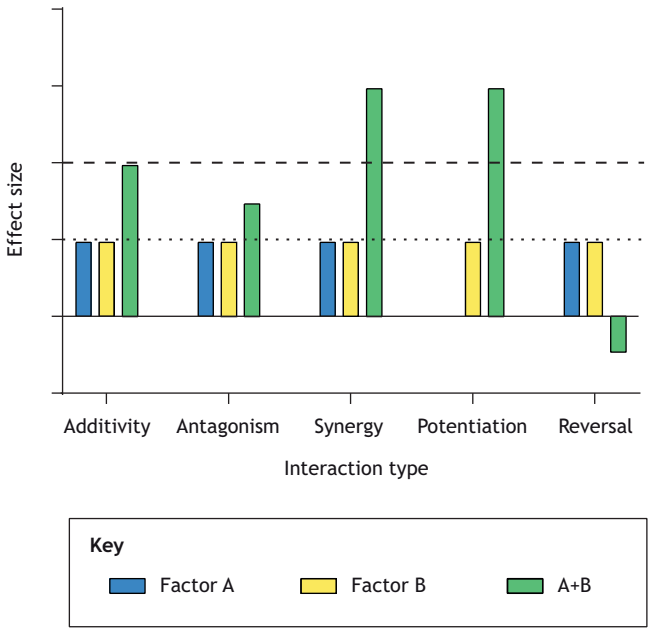

Fig. 3. Types of interactions between multiple stressors based on the relative effects of single and combined factors. The dotted line indicates the individual effect size of factors A and B applied separately, and the dashed line shows the sum of the effects of the individual factors. Additive interactions occur when the effect size of combined factors equals the sum of the effects of individual factors. Antagonism and synergy occur when the effects of combined factors are less (antagonism) or greater (synergy) than expected in the case of additivity. Potentiation occurs when one of the factors that has no effect when applied individually, enhances the effect of another factor when applied in combination. Effect reversal describes the situation when the direction of the combined impact of two factors is opposite to the direction of the factors' effects when applied individually.

generally recognized potential of bioenergetics approaches for mechanistic predictions of multiple stressor interactions (Goussen et al., 2020; Matzelle et al., 2015; Segner et al., 2014; Sokolova, 2013; Sokolova et al., 2012), this field of ecological theory and application remains in its infancy. Recent studies, however, show that bioenergetics-based approaches can provide useful insights into the nature, outcomes and mechanisms of stressor interactions (Goussen et al., 2020; Matzelle et al., 2015; Van Dievel et al., 2019). For example, joint exposure to predation risk and a pesticide revealed that the additive effects of these stressors on survival and development of damselflies are probably mediated by bioenergetics disturbances, with the predation risk suppressing energy assimilation, and chlorpyrifos exposure reducing the energy conversion efficiency and increasing basal ATP demand (Van Dievel et al., 2019). In largemouth bass, the bioenergetics impacts of chemical stress (exposure to a pesticide) and natural stressors (temperature and food availability) were best explained by the additive model, albeit the magnitude of the pesticide impact was trivial compared with the effects of the natural variability in temperature and food (Beyers et al., 1999). Energy-based modeling also adequately captured the effects not only of single factors but also two- and three-factor combinations (including temperature, food density and chemical stress) in freshwater daphnids (Goussen et al., 2020).

Below, I outline two complementary approaches to explore bioenergetics-based responses to environmental stress and stressor interactions: a quantitative (modeling) approach based on the ecological production models, and a qualitative (biomarker-based) approach to determine transitions from the optimal to the pejus and pessimum range. The modeling approach is especially useful for prediction of population dynamics including changes in abundance and biomass over time, whereas the biomarker-based assessments can assess potential shifts in species distribution by identifying the range of habitats and environmental conditions compatible with long-term survival of the population.

Bioenergetically based models to predict the individual and population level impacts of multiple stressors

Bioenergetics-based models that predict biomass production depending on energy intake and expenditure have a long history in aquatic physiological ecology (Bayne et al., 1979; Deslauriers et al., 2017; Widdows and Johnson, 1988; Winberg, 1956). These models quantify the energy flux through the organism based on the general energy balance equation:

$$P = C - \mathrm{SDA} - R - A - W, \quad (1)$$

where P (in J day^{-1}) is the amount of energy invested in production (somatic and gonadal growth), C is the amount of energy consumed, SDA is the energy required for digestion measured as the specific dynamic action, R is energy lost in respiration (indicative of the basal maintenance costs), A is energy invested in activity and mechanical work, and W is energy lost in wastes (including feces and nitrogen excretion).

Traditional bioenergetics models such as the scope for growth (SFG) model originally developed for bivalves (Bayne et al., 1979; Rodhouse et al., 1986; Widdows and Johnson, 1988) and the Wisconsin fish model (Deslauriers et al., 2017; Hewett, 1992) have been used to evaluate the effects of diet or environmental constraints on growth, optimize the maintenance conditions for aquaculture, and predict the effects of environmental shifts and human interventions on species productivity (Deslauriers et al., 2017; Domínguez et al., 2020; Fly and Hilbish, 2012; Holt and Jørgensen, 2015; Lefevre et al., 2017; Louis et al., 2019; Nisbet et al., 2012; Wang et al., 2015). These models provide an excellent tool to assess the impacts of multiple stressors on the organismal fitness by measuring the fundamental vital rates (such as food uptake and assimilation, respiration and excretion) of an organism under different stress scenarios and quantifying the scope for performance (SFP; Fig. 2) based on these measurements:

$$\mathrm{SFP} = P + A = C - \mathrm{SDA} - R - W. \quad (2)$$

Recently, new bioenergetics-based models have been developed, including the dynamic energy budget (DEB) model (Kooijman, 2000). The mathematical structure and parameter estimation of DEB has been extensively reviewed in recent years (Alunno-Bruscia et al., 2011; Baas et al., 2010; Jager et al., 2010; Jusup et al., 2017; Kooijman, 2010; Kooijman et al., 2009, 2020; Marques et al., 2018) and will not be described here. Broadly, the DEB model quantifies the allocation of assimilated energy into two major fluxes, one including somatic growth and maintenance, and another involving reproduction, maturation and associated maintenance costs. In the standard DEB model, the assimilated energy flux is divided between these two branches according to the so-called kappa rule, assuming that a fixed fraction (κ) of the energy flux is directed towards the somatic branch with the remainder ($1 - \kappa$) allocated to reproduction (van der Meer, 2006). Similar to the traditional production models such as the SFG or Wisconsin model, the DEB predicts a decrease in organismal fitness with increasing maintenance costs due to multiple stressors (Accolla et al., 2020;

Goussen et al., 2020). Mathematical formality combined with explicit mechanistic physiological foundation and the ability to separately quantify investments into somatic growth and reproduction make the DEB model an excellent choice for ecological predictions of population growth under different stress scenarios (Goussen et al., 2020). However, the high degree of mathematical abstraction and the large number of model parameters (11 in the standard DEB model) introduce a barrier for broad applicability of the DEB model to multiple species and environmental contexts (Jusup et al., 2017). These problems are recognized by the DEB theorists and users, and are addressed by analysis of the parameter estimability (Saraiva et al., 2011; van der Meer, 2006; van der Veer et al., 2006) and creation of an open database of the DEB parameter estimates for multiple species (Add-My-Pet database) (Kooijman et al., 2020; Marques et al., 2018). Despite the advancement of the DEB models, the usefulness of traditional production models should not be under-estimated as they can quantify the stress-induced loss of fitness using experimentally amenable measurements of the vital rates (Albentosa et al., 2012; Baillieul et al., 2005; Di Santo, 2016; Ericson et al., 2010; Louis et al., 2019; Moore et al., 2006; Wang et al., 2015) and generate similar predictions to the DEB (Barillé et al., 2011; Filgueira et al., 2011; Nisbet et al., 2012).

Quantification of the energy fluxes using DEB or traditional production models provides a simple means to test the additive null-model of stressor interactions and determine the underlying mechanisms of possible deviations from additivity (Fig. 3). Thus, additivity might be expected in the pejus range for the combined effects of the two stressors that individually increase the energy demand, but interactions can become synergistic or antagonistic in the pessimum range due to the limitations of W_{max} and/or transition to the metabolically arrested state. Furthermore, stressors that negatively affect W_{max} might exhibit non-additive interactions due to conflicts between the elevated ATP demand for homeostasis maintenance and lower capacity for ATP production. The specific outcome of the stressor interactions would in this case depend on the degree of W_{max} suppression relative to ATP demand, with increasing probability of non-additive interactions when ATP demand becomes close to, or exceeds, W_{max}. Future studies are needed to test these hypotheses and explore the role of bioenergetic mechanisms in the occurrence of 'ecological surprises' due to non-additive stressor interactions.

Biomarkers of stress-induced bioenergetic state transitions

Qualitative biomarkers related to organismal energy status can be used to detect the transition between different stressor ranges (optimum, pejus, pessimum and lethal) (Fig. 2B) and assess the range of environmental conditions compatible with population survival. The determination of the pejus–pessimum transition is especially important for the prediction of population-level outcomes, as the bioenergetically unsustainable state in the pessimum range precludes long-term population persistence.

Standard metabolic rate

An increase of SMR above normal baseline indicates a shift into the pejus range, whereas SMR approaching W_{max} marks transition into the pessimum range (Fig. 2B). In stress-tolerant species that enter the metabolically depressed state during extreme stress, transition to the pessimum involves a simultaneous decrease in SMR and W_{max}, so that SMR$\approx W_{max}$ and all energy and metabolic capacity is devoted to survival (Fig. 2B). Using SMR (typically measured as oxygen consumption rate of the resting organism in the post-prandial state) as a marker of transition into the pejus or pessimum state thus requires knowledge of the respective species-, life stage- and temperature-specific baselines, and rests on the assumption that most ATP of an organism is generated aerobically. This assumption is violated in the pessimum range where the anaerobic pathways contribute to ATP production and resting $\dot{M}_{O_2}$ under-estimates the SMR. This limitation can be overcome by using direct calorimetry to capture both aerobic and anaerobic contributions to energy flux (Kaiyala and Ramsay, 2011). Furthermore, elevated rates of anaerobic metabolism can serve as an indicator of transition into the bioenergetically unsustainable pessimum state (Fig. 2B) and can be detected by comparing the heat fluxes calculated from the $\dot{M}_{O_2}$ and measured by direct calorimetry (Kaiyala and Ramsay, 2011) or by measuring the accumulation of anaerobic end products (Grieshaber et al., 1994).

Energy reserves

Deposition of energy storage molecules (glycogen, lipids and proteins) plays a crucial role in buffering periods of food shortage (and thus potentially negative SFP) and provisioning for non-feeding life stages such as lecithotrophic embryos and larvae. Energy reserves are highly dynamic throughout the life cycle, accumulating in periods of food abundance and relative metabolic rest and diminishing during starvation or high energy demand, e.g. for reproduction (Arts et al., 1992; Benomar et al., 2009; Fernandes and McMeans, 2019; Haider et al., 2020; Hawkins et al., 1985; Sánchez-Paz et al., 2006). Stress exposures typically lead to the depletion of tissue energy stores due to mismatch between organismal energy demand and energy supply from the environment (Sokolova, 2013; Sokolova et al., 2011). Sustained loss of energy reserves indicates transition into the pessimum range and results in diminished fitness and eventually mortality. Therefore, a decrease in energy reserves below the normal life stage- and population-specific baseline is an indicator of the pessimum range.

Energy uptake

Abiotic stressors such as temperature, hypoxia, ocean acidification or pollution commonly suppress energy intake due to behavioral changes affecting feeding rates, physiological shifts altering the digestive processes and energy assimilation, or both. A decrease in energy uptake might be expected outside the optimum range of the population, but whether such a decrease commonly occurs in the pejus or only in the pessimum range requires further investigation. Given that the energy assimilation rate sets the upper limit for all downstream energy fluxes (Fig. 1A), it is highly recommended that energy uptake and assimilation rates are included in assessments of the bioenergetics effects of multiple stressors.

Mitochondrial capacity

Mitochondria play a key role in stress responses due to their multifarious roles as an ATP-producing organelle and the cellular hub for stress sensing and signaling (Sokolova, 2018; Sokolova et al., 2019). Environmental stressors can strongly affect mitochondrial ATP synthesis capacity, efficiency of ATP production, and generation of potentially toxic ROS (Sokolova, 2018; Sokolova et al., 2019). Furthermore, mitochondrial stress can result in the release of signaling molecules that induce the adaptive stress response in the cell, communicate stress to other cells and tissues and, in extreme cases, initiate programmed cell death (Sokolova, 2018; Sokolova et al., 2019). Unfortunately, the functional assessment of mitochondrial activity and ROS production is time and labor intensive, and requires isolation of

organelles or permeabilized cells from fresh tissues. Some biochemical approaches (such as measurement of ETS system activity using assays based on the reduction of tetrazolium dyes) can provide useful surrogates (Berridge et al., 2005; Owens and King, 1975). ETS activity measured by these assays positively correlates with whole-organism $\dot{M}_{O_2}$ (Owens and King, 1975; Verslycke and Janssen, 2002; Verslycke et al., 2004) and can serve as a proxy for the maximum capacity of ATP synthesis in an organism (Chamberlin, 2004a,b; Ivanina et al., 2012, 2016; Kurochkin et al., 2011) and contribute to the assessment of W_{max}.

Protein synthesis

Protein synthesis rates are sensitive to environmental stressors and highly responsive to changes in cellular energy status due to the high energy cost of protein biosynthesis (Guppy and Withers, 1999; Hulbert and Else, 2000). Elevated protein synthesis rates are commonly found in the pejus range of environmental stressors, reflecting production of protective proteins such as HSPs, detoxification and anti-oxidant enzymes (Pan et al., 2015; Sokolova and Lannig, 2008; Sokolova et al., 2011). Transition to the pessimum environmental range is associated with suppression of overall protein synthesis, even though selected proteins such as HSPs are still produced (Storey, 1998; Storey and Storey, 2004). Multiple proxies are available to assess rates of protein synthesis, including the RNA:DNA ratio (Chícharo and Chícharo, 2008; Haines, 1973), incorporation of labeled amino acid precursors into newly synthesized proteins (Bonifacino, 2001) or use of specific inhibitors of protein synthesis to determine the fraction of respiration accounted for by protein synthesis (Cherkasov et al., 2006; Ivanina et al., 2020; Pace and Manahan, 2006; Pan et al., 2015). Assessment of the molecular switches of protein biosynthesis (such as levels of reversible phosphorylation of transcription initiation and elongation factors) can also be useful (Baird and Wek, 2012; Kenney et al., 2014), albeit application of these methods to non-model organisms is limited by the availability of cross-reactive antibodies against the respective proteins (Ivanina et al., 2016; Larade and Storey, 2002, 2007; Madelaire et al., 2020; Ramnanan et al., 2009). In recent years, the method toolbox for measuring rates of protein synthesis has expanded to include approaches based on mass spectrometry, non-radioactive labeling and ribosome profiling (Iwasaki and Ingolia, 2017), but these approaches as yet await implementation in non-model species of aquatic ectotherms.

Conclusions and outlook

The conserved nature and high ATP cost of the general cellular stress response underscore the usefulness of bioenergetics in assessing the effects of multiple stressors and predicting their ecological consequences for populations. Both quantitative (modeling) and qualitative (biomarker-based) approaches can help determine the physiological tolerance limits in populations facing multiple stressors and assess the habitability of different environments to animals based on their ability (or lack thereof) to maintain a positive energy balance. Knowledge of the energetic basis of population growth is necessary (albeit not sufficient) to form reliable predictions of population dynamics and to determine the biogeographic distribution ranges of a species during environmental shifts (Deutsch et al., 2015; Kooijman et al., 2020). Future developments of bioenergetics approaches to achieve such predictions requires incorporation of the effects of biotic interactions (such as the presence of predators or competitors) on individual bioenergetics (Rakel et al., 2020). Furthermore, models need to include time-resolved energy fluxes to account for life-cycle and seasonal variations in energy intake, expenditures and allocation priorities, as well as metabolic effects of aging. Delayed energy costs during recovery after extreme stress as well as the allostatic load (the costs of repairing wear and tear due to repeated stress exposures) need to be quantified for a broad range of organisms and stressors, and the duration of the periods (relative to the organism's life cycle) that can be withstood at zero or negative SFP need to be determined. Bioenergetics assessments of populations from different parts of a species' distribution range will also provide important insights into the role of energy fluxes in shaping population dynamics in the central–marginal continuum and between sink and source populations in complex metapopulations. Advancement of molecular tools that help us to understand the links between cellular energy deficiency and general stress response should yield new sensitive biomarkers for determining ecologically important bioenergetics transitions using molecular proxies. Ecological bioenergetics is thus a ripe field for current applications and future discoveries that link the molecular-to-ecosystem level energy fluxes in the multi-stressor landscape in a mechanistic, predictive and ecologically relevant framework.

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Competing interests

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