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Interactive effects of metal pollution and temperature on metabolism in aquatic ectotherms: implications of global climate change

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ABSTRACT: In light of the current rising mean temperatures and fluctuations in temperature extremes involved in global climate change, a cause-and-effect understanding of the temperature-dependent impacts of additional environmental stressors on marine life is crucial for the elaboration of how marine ecosystems will shape in the future. The thermal environment plays a direct role in the distribution and survival of marine ectotherms through the temperature-dependent effects on their physiology, as well as indirectly by affecting the organism's susceptibility to other biotic and abiotic stressors. We review studies that have investigated the effects of temperature and anthropogenic pollution by trace metals, with a focus on metabolic regulation as a major mechanism that underlies the interactive effects of temperature and metals on the physiology and survival of ectotherms. These studies suggest that impairment of energy metabolism plays a key role in the synergistic effects of these stressors, and we elaborate a mechanistic framework for understanding these interactions. Furthermore, the present study seeks to provide an impetus for future investigations in order to define more precisely the physiological mechanisms and functional properties of temperature–pollution interactions.

KEY WORDS: Marine ecosystems · Global warming · Trace metals · Energy metabolism · Stress tolerance · Mitochondria

1. METAL POLLUTION AND CLIMATE CHANGE

Global climate change, which is largely driven anthropogenically, has become a dire reality in the past century, and its impact is expected to increase in the future. Recent models predict a 0.2°C increase in the mean global temperature per decade in the next 2 decades and a 1.8 to 4°C increase by the year 2100 (IPCC 2007). A rise in global temperature is accompanied by increased temperature fluctuations and frequency of temperature extremes (Trenberth et al. 2007 and references therein). Global climate change is already taking its toll in the biosphere, leading to significant changes in species distribution and abundance around the globe. A less-than-exhaustive list of such recent climate-driven changes include major faunal shifts and changes in marine habitats (e.g. Beaugrand 2004), declines and shifts in zooplankton abundance (e.g. Reid et al. 1998), extensive bleaching of coral reefs (e.g. Hoegh-Guldberg 1999, Suzuki et al. 2007), local extinctions of populations (e.g. Helmuth et al. 2002), increases in mosquito-borne diseases in highlands (e.g. Martens et al. 1999), expansions of invasive species (e.g. Occhipinti-Ambrogi 2007) and the poleward shift of ranges of birds and non-migratory insects (e.g. Austin & Rehfish 2005, La Sorte & Thompson 2007) (for review see also Roessig et al. 2004, Parmesan 2006, Fischlin et al. 2007, Rosenzweig et al. 2007).

Aquatic ecosystems are vulnerable to the effects of global climate change, because the vast majority (>95%) of species in aquatic realms are ectotherms (Willmer et al. 2000). Environmental temperature plays

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a key role in the physiology of ectotherms, as their body temperature changes with the temperature of the environment, resulting in corresponding alterations of the rates of all physiological and biochemical reactions and stability of biological molecules (Hochachka & Somero 2002). Paleontological records, as well as the recent history of global warming, demonstrate that even modest changes in environmental temperature by a few degrees centigrade result in major shifts in ectotherm distributions and in mass extinctions of their populations (Hochachka & Somero 2002, Gómez et al. 2008). Ectotherms are key components of aquatic food chains, spanning the range of ecological functions from primary producers to top-level consumers (Willmer et al. 2000, Begon et al. 2006); therefore, changes in population abundance and dynamics of these species due to global climate change will have profound 'ripple' effects for the whole ecosystem. Moreover, the most productive areas in aquatic realms, including freshwaters, estuaries, coastal waters and internal seas, are also those that are expected to experience the strongest impact of global warming (Willmer et al. 2000, Lozano et al. 2004).

Estuarine and coastal areas are often the most polluted areas in the ocean, due to urban development and human industrial and agricultural activities (Clark 2001, Hyun et al. 2006 and references therein; see also www.oceansatlas.com/unatlas/-ATLAS-/chapter 12f.html). Anthropogenic disturbances in these ecosystems mean that their inhabitants have to cope with multiple stressors, including pollution, hypoxia, eutrophication, etc., in addition to the temperature stress resulting from global climate change. Therefore, an understanding of the interactive effects of multiple stressors (such as pollutants and temperature) and their mechanisms is critical for predicting the tolerance limits, survival and productivity of ectotherm populations and for modeling the effects of global climate change on aquatic ecosystems (especially those with high anthropogenic pressure) around the world (Vinebrooke et al. 2004, Adams 2005).

To date, a few reviews describe the effects of temperature on endpoints such as toxicity (especially mortality), uptake and accumulation of pollutants (Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002, Gordon 2005, Rainbow 2007). However, they do not systematically deal with the physiological background of interactions between temperature and pollutants, partially, due to the relative dearth of physiological studies on the combined effects of pollutants and temperature, and partially due to the fact that these reviews look at the broad variety of organic and inorganic pollutants that differ greatly in their mechanisms of action. As a result, an integral picture of the temperature–pollutant interaction on ectotherm physiology is hard to come by unless researchers focus on groups of pollutants with similar toxic mechanisms. Such studies would be critical for our understanding of the physiological mechanisms that limit species distribution in polluted environments in the face of global climate change, and for our ability to make generalizations beyond individual sentinel species.

Trace metals are important persistent pollutants in aquatic ecosystems worldwide and are especially prevalent in freshwater, estuarine and coastal marine ecosystems exposed to high degrees of urban pressure (Lau et al. 1998, de Mora et al. 2004, Hyun et al. 2006). Moreover, recent studies indicate that human activities significantly affect trace metal levels even in remote parts of the globe traditionally considered pristine, such as the Arctic and Antarctic (Bargagli 2000, Sanchez-Hernandez 2000). Out of the top 20 hazardous substances on the EPA CERCLA Priority List of Hazardous Substances for 2005, 5 are metals (US Agency for Toxic Substances and Disease Registry, available at www. atsdr.cdc.gov/cxcx3.html#bookmark02), as are 8.5% of the priority pollutants for the EPA Clean Water Act (available at http://oaspub.epa.gov/wqs/wqsi_epa_ criteria.report). Metals can accumulate in aquatic organisms and are easily transferred through the food chain to the top consumers, including humans (see Wallace & Lopez 1996, 1997, Wallace & Luoma 2003, Wallace et al. 2003, Fisk et al. 2005 and references therein). In some cases, such as for methylmercury (MeHg), biomagnification also occurs along the food chain, enhancing the toxic effects (Atwell et al. 1998, Campbell et al. 2005). Although the toxicity and associated health hazards of different metals may vary, many metals have common toxic cellular mechanisms and elicit similar protective responses in a wide variety of organisms (reviewed by Byczkowski & Sorenson 1984, Roesijadi & Robinson 1994, Wallace & Starkov 2000, Coyle et al. 2002, Valko et al. 2005, Amiard et al. 2006).

In this review, we focus on an analysis of the current state of knowledge about the interactive effects of trace metals and temperature on the physiology of aquatic ectotherms, with emphasis on metabolic regulation and its major role in the underlying interactions between these stressors. Despite the fact that the energy costs of metal toxicity are widely debated in the literature (Sibly & Calow 1989, Calow & Forbes 1998, van Straalen & Hoffmann 2000, Roff 2002), the bioenergetic aspects of temperature–metal interactions in aquatic ectotherms have not been extensively studied (see Sokolova 2004, Lannig et al. 2006, 2008 and references therein) and are only briefly (if at all) discussed in recent general treatises on mechanisms of metal toxicity (e.g. Malins & Ostrander 1994, Walker et al. 2001, Landis & Yu 2003, Gordon 2005). This review intends draw attention to metal toxicity and temperature–

metal interactions. We summarize current findings and hypotheses pertaining to the bioenergetic aspects of temperature–pollution interactions and their consequences to both the metal toxicity and temperature tolerance, and create a physiological framework for understanding the mechanisms of these interactions, and we outline future research directions in this area.

2. TEMPERATURE EFFECTS

An observation that environmental temperature can affect tolerance to trace metals in aquatic ectotherms is one of the earliest findings in ecological toxicology (Cairns et al. 1975 and references therein). In principle, there are several potential types of temperature–toxicity relationships described for different pollutants and toxins (Fig. 1), where toxicity endpoints can be either lethal (e.g. mortality), or non lethal (e.g. decrease in physiological performance, growth rate, enzyme activity). Typically, temperature–toxicity relationships for metals follow the Type I and II curves on Fig. 1, so that elevated temperatures tend to enhance toxic effects of metals on organisms (Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002, Gordon 2005, present review). Indeed, published studies (reviewed in Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002, and Table 1 in the present paper) indicate that an increase in environmental temperature results in elevated mortality rates in metal-exposed ectotherms in 80% of the cases (N = 118) (Fig. 2).
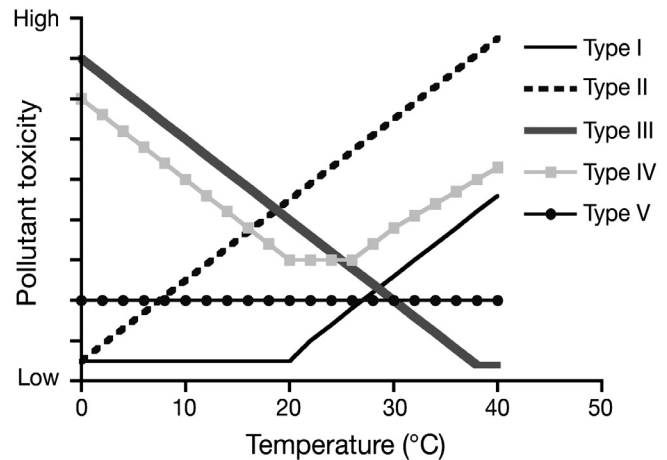

Fig. 1. General patterns of pollutant toxicity as a function of ambient temperature in aquatic ectotherms (modified and updated from Weihe 1973). Type I and II responses are the most typical for trace metals when toxicity increases with increasing temperature (see Section 2 for details). Type III response (decreasing toxicity with increasing temperature) has been described for some organic pollutants such as DDT (Cairns et al. 1975), but rarely for metals. Type IV (optimum response) is often found in mammals when pollutant or drug toxicity is minimal in the thermoneutral zone (Weihe 1973) and may be expected in stenothermal aquatic ectotherms with narrow thermal tolerance windows; however, no data exist for such organisms so far. Type V response is typical for pollutants that have constant toxicity irrespective of the temperature; this response is rarely found in aquatic ectotherms, and if temperature deviates sufficiently from the optimum, the organism is expected to respond according to Type I or Type IV curves

Table 1. Examples of the effect of environmental temperature on metal toxicity (assessed as mortality rates) in aquatic ectotherms. Temperature effect—positive: mortality increases with increasing temperature; negative: mortality decreases with increasing temperature; none: mortality does not change with temperature; optimum: mortality is minimum at the optimum temperature and increases at higher and lower temperatures. Article search was performed in Web of Science and PubMed databases using key words 'temperature' and 'metal toxicity'; only articles discussing aquatic ectotherms and not covered by the earlier reviews (Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002) were selected for this table. TBT: tributyltin

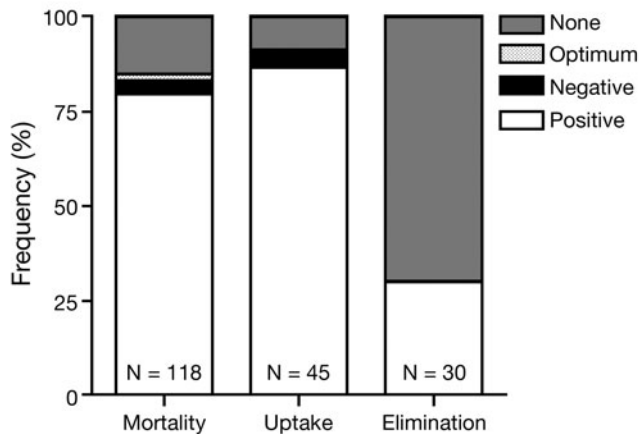|	Species	Metal	Temperature effect	Source
Vertebrates				
Fishes	*Anguilla japonica*	Cd	Positive	Yang & Chen (1996)
Invertebrates				
Plathyhelminthes	*Diplostomum spathaceum*	Cd, Zn	Positive	Morley et al. (2001)
Annelids	*Tubifex tubifex*	Cd, Cr, Pb, Zn, Hg, Cu	Positive	Rathore & Khangarot (2002)
		Mn, Fe	None	Rathore & Khangarot (2002)
Arthropods	*Tigriopus japonicus*	Cu, Sn (as TBT)	Positive	Kwok & Leung (2005)
	Diaptomus clavipes	Cu	Positive	Boeckman & Bidwell (2006)
	Daphnia pulex	Cu	None	Boeckman & Bidwell (2006)
	Daphnia magna	Hg	Positive	Tsui & Wang (2006)
		Cr	Positive	Martínez-Jerónimo et al. (2006)
		Cd	Positive	Heugens et al. (2003)
	Orconectes immunis	Cu, Cd, Zn, Pb	Positive	Khan et al. (2006)
Mollusks	*Gammarus pulex pulex*	Cu, Zn, Pb	Positive	Bat et al. (2000)

Fig. 2. Temperature effects on uptake/accumulation, elimination and toxicity (measured as mortality) of trace metals in aquatic ectotherms. Frequencies of occurrence of different types of correlations between environmental temperature and the respective endpoint are given in percentage. Positive: uptake or accumulation (U), elimination (E), or mortality (M) increase with temperature; negative: U, E or M decrease with temperature; optimum: U or M is minimal (or E is maximal) at the optimal temperature and rises (or for E, declines) as the temperature increases or decreases; none: no correlation observed between temperature and the respective endpoint. Based on Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002, and Tables 1 to 3 of the present paper

The elevated toxicity of metals at higher temperatures may be partially explained by the higher uptake rate (and thus high internal concentrations) of metals. Typically, the rates of metal uptake and accumulation increase with increasing temperature (Cairns et al. 1975, McLusky et al. 1986, Hutchins et al. 1996, Heugens et al. 2002, and Table 2 of the present review). Q_{10} for metal uptake ranges between 3 and 5, occasionally up to 7 to 12 (meaning a 3- to 5-fold and 7- to 12-fold increase in uptake rate, respectively, with every 10°C increase in environmental temperature [Hutchins et al. 1996]). Indeed, metal uptake and accumulation were strongly elevated at high temperatures in >85% of all studies analyzed for this review (Fig. 2), covering a broad variety of aquatic organisms from protozoans to flatworms and vertebrates, suggesting that highly conserved physiological and cellular processes underlie the temperature-dependent increase in metal uptake and accumulation.

Bioavailability of metals may strongly affect their uptake and toxicity in aquatic organisms (Rainbow 2007). Dissolved free metal ions are the most bioavailable form in aquatic environments, with the fastest rate of uptake and accumulation in organisms (Luoma 1983, Worms et al. 2006). In principle, the environmental temperature can affect the bioavailability of metals due to the higher solubility of metal compounds, and thus higher concentrations of free metal ions, at ele-

vated temperatures. However, empirical data, as well as 2 widely used models (the free ion activity model and the biotic ligand model), show that temperature in the environmentally relevant ranges has a negligible effect on metal speciation, particularly on free ion activity (Luoma 1983, Bervoets & Blust 1999, Hassler et al. 2004). Therefore, the biological effects of temperature need to be taken into account in order to explain its effect on metal uptake and accumulation.

In principle, several biological factors can affect temperature-dependent changes in metal uptake and/or elimination, including metal transport, membrane permeability and systemic functions (such as ventilation or absorption from food) that can influence the degree of exposure of permeable epi- and endothelia to metals. Cellular pathways for the uptake and elimination of metal ions in the cell include passive diffusion across cell membranes, facilitated transport, active transport by ion channels, and endocytosis (for recent reviews on metal transport mechanisms see Ponka et al. 1998, Rolfs & Hediger 1999, Wood et al. 1999, Zalups & Ahmad 2003, Kambe et al. 2004, Balamurugan & Schaffner 2006). Uptake rates by passive diffusion are low for most dissolved metals because their charges and hydration shells make them poorly soluble in lipid membranes; the few exceptions are metallo-organic complexes such as MeHg or tributyltin (TBT) (Roesijadi & Robinson 1994, Walker et al. 2001). Moreover, temperature-dependent changes in diffusion coefficients are usually small, and typical Q_{10} values for passive diffusion are in the range of 1.03 to 1.40 (Willmer et al. 2000), which does not sufficiently explain the temperature dependency of metal uptake rates in most organisms (Bervoets et al. 1996, Hutchins et al. 1996). Similarly, receptor-mediated endocytosis plays a limited role in the uptake of trace metals, with an exception of some essential metals such as iron (Roesijadi & Robinson 1994, Ponka et al. 1998). Active ATP-dependent transport via ion pumps and facilitated diffusion via ion channels are by far the predominant routes of metal uptake in aquatic organisms (Roesijadi & Robinson 1994, Rolfs & Hediger 1999, Wood et al. 1999, Zalups & Ahmad 2003, Kambe et al. 2004, Balamurugan & Schaffner 2006), which, in ectotherms, are strongly affected by the environmental temperature. Indeed, the apparent activation energies (E_a) for metal uptake are typically much higher than activation energies for free diffusion and are close to E_a for respiration and active ion transport (Bervoets et al. 1996, Hutchins et al. 1996). Therefore, a rise in temperature will result in a profound increase in metal uptake rates and, unless counteracted by a similar increase in elimination rates, an elevated accumulation of metals in the organism.

An increase in metabolic rates at elevated temperatures may contribute to metal accumulation in ectotherms due to a higher energy demand. This increased

Table 2. Examples of the effect of environmental temperature on metal uptake and accumulation in aquatic ectotherms. Temperature effect—positive: uptake/accumulation increases with increasing temperature; negative: uptake/accumulation decreases with increasing temperature; none: uptake/accumulation does not change with the temperature. Unless otherwise indicated, uptake/accumulation of waterborne metals by whole organisms is presented. An article search was performed in Web of Science and PubMed databases using key words 'temperature' and ('metal uptake' or 'metal accumulation'); only articles discussing aquatic ectotherms and not covered by the earlier reviews (Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002) were selected for this table

	Species	Metal	Temperature effect	Uptake or accumulation	Source
Vertebrates					
Fishes	*Oncorhynchus mykiss*	Ag	Positive	Uptake, accumulation	Nichols & Playle (2004)
	Salmo gairdneri	Hg	Positive	Accumulation	McLeod & Pessah (1973)
		Cd	Positive	Accumulation	Roch & Maly (1979)
	Lepomis macrochirus	Cu	Positive	Accumulation	Felts & Heath (1984)
	Anguilla japonica	Cd	Positive	Accumulation	Yang & Chen (1996)
Invertebrates					
Mollusks	*Saccostrea echinata*	Cd, Zn	Positive	Accumulation	Denton & Burton-Jones (1981)
	Crassostrea virginica	Cd	None	Accumulation	Lannig et al. (2006)
		Cd	Positive	Accumulation	Cherkasov et al. (2007)
	Mytilus edulis	Cd	Positive	Accumulation	Phillips (1976)
		Cd, Co, Zn	Positive	Uptake	Baines et al. (2005)
		Ag, Am	None	Uptake	Baines et al. (2005)
		Cd	Positive	Accumulation	Fischer (1986)
		Cd, Pb	Positive	Uptake	Mubiana & Blust (2007)
		Cu	Negative	Uptake	Mubiana & Blust (2007)
		Co	None	Uptake	Mubiana & Blust (2007)
	(isolated gills)	Cd, Pb, Cu, Co	Positive	Uptake	Mubiana & Blust (2007)
	Nucella lapillus	Cd	Positive	Accumulation	Leung et al. (2000)
	Perna viridis	Cd, Zn	Positive	Uptake	Wang et al. (2005)
Arthropods	*Callinectes sapidus*	Cd	Positive	Accumulation	Hutcheson (1974)
	Daphnia magna	Cd	Positive	Accumulation	Heugens et al. (2003)
		Hg	Positive	Uptake	Tsui & Wang (2006)
	Chironomus riparius (larvae)	Cd, Zn	Positive	Uptake	Bervoets et al. (1996), Bervoets & Blust (1999)
	Hexagenia rigida (larvae)	MeHg	Positive	Accumulation	Odin et al. (1996)
		Cd	Negative	Accumulation	Odin et al. (1996)
Echinoderms	*Ophiothrix fragilis*	Ag, Am, Ba, Cd, Co, Cs, Eu, Mn, Ru, Zn	Positive	Uptake	Hutchins et al. (1996)
Chlorophyta	*Chlorella vulgaris*	Cu	Positive	Uptake	Mehta et al. (2002)

demand results in elevated ventilation and/or feeding rates (Willmer et al. 2000, Pörtner 2001, 2002), which in turn lead to higher exposure to metal-contaminated water or food. Moreover, metal contamination can damage the respiratory surfaces in aquatic ectotherms such as fish, crustaceans and bivalves, resulting in a less efficient oxygen uptake and an associated higher need for active ventilation (Spicer & Weber 1991, Nonnotte et al. 1993, Wilson & Taylor 1993, Hebel et al. 1997, Leung et al. 2000 and references therein). For example, the proportion of time spent actively ventilating increased with increasing temperatures and Cd exposure in eastern oysters *Crassostrea virginica*; at 20°C oysters spent about 30% of time actively ventilating, whereas at 28°C oysters exposed to Cd spent >70% of time ventilating (Lannig et al. 2006). Cd and Zn uptake rates were closely correlated with the rate of oxygen consumption ($\dot{M}O_2$) and ventilation rates in green mussels *Perna viridis* over a wide range of environmental temperatures and O_2 partial pressures (Wang et al. 2005). Other studies in bivalves also demonstrate that ventilatory activity may be a rate-limiting step in metal uptake in these organisms (Massabuau & Tran 2003). In fish, such as bluegills and rainbow trout, high venti-

lation rates at elevated temperatures also resulted in higher uptake of metals such as Cd, Cu and Hg (McLeod & Pessah 1973, Roch & Maly 1979, Felts & Heath 1984). Temperature effects on metal uptake from food have been less extensively studied (Roesijadi & Robinson 1994, Baines et al. 2005). Given the high transfer rate of trace metals across digestive tract epithelia (Baines et al. 2005, Cooper et al. 2006, Croteau et al. 2007 and references therein), a dietary uptake of metals may represent an important exposure route for aquatic ectotherms, and temperature-dependent changes in food intake and absorption may play a key role in metal accumulation, toxicity and food web transfer and thus require further investigation.

The effect of temperature on membrane permeability to metal ions represents another intriguing mechanism that may contribute to elevated metal uptake by aquatic ectotherms. An acute change in ambient temperature results in a change in membrane fluidity and local transitions of the lipid bilayer between the sol and gel phases, which can affect membrane integrity and permeability, as well as the mobility and function of membrane-associated receptors, transport and channel proteins (Hazel 1995, Hochachka & Somero 2002). If the temperature change persists, membrane structure and properties may change in the long term, in order to counteract alterations in membrane order (Hazel 1995, Hochachka & Somero 2002). Usually, adaptation or acclimation to low temperatures results in an increase in the content of phospholipids with unsaturated acyl chains, a decrease in the ratio of phosphatidyl choline to phosphatidyl ethanolamine and a decline in cholesterol content in the membrane, all making the membrane more fluid (less viscous) (Hazel 1995, Hochachka & Somero 2002). Acclimation or adaptation to high temperatures leads to the opposite changes in phospholipid and cholesterol structure and content (Hazel 1995, Hochachka & Somero 2002). These homeostatic changes, first described by Sinensky (1974), are often referred to as homeoviscous adaptation, emphasizing that their net effect is to maintain the optimum level of fluidity compatible with the normal function of the membrane and associated structures (Hazel 1995, Yang & Hwang 1996, Crockett 1998, Farkas et al. 2001). Potentially, homeoviscous adaptation in aquatic ectotherms during long-term temperature change (e.g. due to seasonality or adaptation to different climates), as well as acute alterations of membrane fluidity during short-term (e.g. diurnal or tidal) temperature fluctuations, can have profound effects on membrane permeability (Williams & Somero 1996, Hall et al. 2002, Pernet et al. 2007) affecting metal uptake; however, this aspect of membrane physiology has not been extensively explored and would represent a fruitful avenue for further investigations.

Temperature effects on metal elimination in aquatic ectotherms have been less extensively studied than metal uptake, and available data suggest that these effects are less important and profound than temperature effects on the uptake (Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002, Gordon 2005, Table 3 in the present review). Indeed, most studies detected only a weak temperature dependence of metal elimination, and in most cases elimination rates were temperature-independent in the environmental range (Fig. 2). Mechanisms of metal elimination in aquatic ectotherms are not well understood. In principle, they may involve passive and active processes similar to metal uptake (Roesijadi & Robinson 1994, Rainbow 2007); however, relative contributions of specific cellular mechanisms to metal elimination and detoxification may differ from those involved in the uptake and require further investigation. As a result of differences in temperature sensitivity of metal uptake and elimination, the net accumulation of metals (and thus internal effective concentrations) increases with elevated temperatures, resulting in higher toxicity (Rainbow 2007). Metal toxicity is determined mostly by the amount of bioavailable metals in the metabolically accessible pool, as well as by the total body burden of the metals (Rainbow 2007). Thus, it is conceivable that environmental temperature can affect metal toxicity without changing the total amount of accumulated metals in the body, if the temperature change results in redistribution of metals between metabolically available (and thus potentially toxic) and unavailable pools (i.e. detoxified or removed to places of long-term storage) (Rainbow 2007). Currently, there are no studies on the effects of environmental temperature on metal distribution between different sub-cellular compartments and/or body organs (e.g. those involved in metal storage vs. metabolism), and this suggestion is speculative at present. It is especially interesting in view of the fact that in some organisms elevated temperatures often appear to result in increased intrinsic sensitivity to metals (i.e. higher toxicity at the same internal concentrations) at elevated temperatures. For example, in rainbow trout, seasonal warming resulted in increased summer mortality without any change in the pollutant concentration (Hg) in the water (McLeod & Pessah 1973). In freshwater crustaceans *Daphnia magna*, median and threshold lethal body burdens of Hg and Cd decreased with increasing temperature, implying that lower tissue metal burdens were required to kill daphnids at higher temperatures (Heugens et al. 2003, Tsui & Wang 2006). Similarly, in eastern oysters *Crassostrea virginica*, exposure to Cd at an elevated temperature (28°C) resulted in a significant increase in mortality compared to 20 or 24°C despite similar tissue Cd burdens at all experimental temperatures (Lannig et al. 2006). Physiological mechanisms

Table 3. Examples of the effects of environmental temperature on metal elimination in aquatic ectotherms. Temperature effect— positive: elimination increases with increasing temperature; negative: elimination decreases with increasing temperature; none: elimination does not change with the temperature. Article search was performed in Web of Science and PubMed databases using key words 'temperature' and 'metal elimination'; only articles discussing aquatic ectotherms and not covered by the earlier reviews (Cairns et al. 1975, McLusky et al. 1986, Heugens et al. 2002) were selected for this table

	Species	Metal	Temperature effect	Source
Vertebrates				
Fishes	*Oncorhynchus mykiss*	Ag	None	Nichols & Playle (2004)
	Noemachelius barbatulus	Cd	Positive	Douben (1989)
	Salmo trutta	Cs	Positive	Ugedal et al. (1992)
Invertebrates				
Arthropods	*Daphnia magna*	Cd	None	Heugens et al. (2003)
	Hexagenia rigida (larvae)	Cd	Positive	Odin et al. (1996)
Mollusks	*Corbicula fluminea*	Hg, Cd	None	Inza et al. (1998)
	Mytilus edulis	Cd, Co, Pb	None	Mubiana & Blust (2007)
		Cu	Positive	Mubiana & Blust (2007)
		Ag, Am, Cd, Zn	Positive	Baines et al. (2006)
		Co	None	Baines et al. (2006)
	Macoma balthica	Am, Co, Cs	None	Hutchins et al. (1998)
Echinoderms	*Ophiothrix fragilis*	Ag, Am, Ba, Cd, Co, Cs, Eu, Mn, Ru, Zn	None	Hutchins et al. (1996)

explaining elevated intrinsic sensitivity to trace metals at high temperatures are not fully understood and may include an increased sensitivity to metals by intracellular structures such as mitochondria and enzymes (Sokolova 2004, Ivanina et al. 2008b), elevated energy misbalance due to increased detoxification and maintenance costs (see Section 3), the redistribution between metabolically available and inert metal pools as suggested by Rainbow (2007), or a combination of these factors. Irrespective of the exact mechanisms, an increased accumulation and toxicity of metals due to elevated temperatures can have important physiological and ecological consequences in aquatic ectotherms, affecting their survival and performance by changing effective concentrations of metals in their tissues an exposure and vulnerability of target organs/systems (Heugens et al. 2003, Tsui & Wang 2006, Rainbow 2007), and potentially resulting in local decreases in abundance and/or extinction of affected populations, and altered transfer rates of metals through the food web (Wallace et al. 2003, Gordon 2005).

3. METABOLIC ASPECTS

Energy metabolism can be regarded as a key target for the stress effects of temperature and toxic metals, due to the key role of energy balance in stress adaptation and tolerance (Sibly & Calow 1989, Calow & Forbes 1998, Roff 2002). Indeed, the survival of an organism under stress conditions crucially depends on its ability to balance energy demand and energy supply (Sibly & Calow 1989, Calow & Forbes 1998, Roff 2002). The minimum requirement for short-term survival is provision of sufficient energy to cover basal maintenance needs such as maintenance of cellular homeostasis and systemic functions, including ventilation and circulation (Sibly & Calow 1989, Calow & Forbes 1998, Pörtner 2001). On a long-term basis (especially on the time scale required for population survival), additional energy is needed to cover other costs, such as reproduction, growth, locomotion (to escape predators, to find food or a mate), etc. (for review see Pörtner 2001). Environmental stressors such as exposure to toxic metals and sub- or supra-optimal temperatures can shift this fine-tuned balance, resulting in energy deficits due to elevated maintenance costs (e.g. for detoxification or repair of the cellular damage by toxins or stressful temperatures) or direct interference with energy conservation (e.g. mitochondrial function and/or cytosolic ATP-producing pathways) (Sibly & Calow 1989, Calow & Forbes 1998, Pörtner 2001, see also Sections 3.1 and 3.2 below). In either case, such shifts in the energy balance may lead to costs and trade-offs at the whole-organism and population levels, resulting in decreased production, elevated mortality and, in extreme cases, local extinctions.

Despite the indubitable importance of bioenergetics in survival under metal and temperature stress, the role of interactive effects of these 2 stressors in energy metabolism has not been extensively explored. Below we critically review the literature on the metabolic effects of temperature–metal interactions and propose approaches that could lead to development of a testable conceptual model that explains how the interactions of elevated temperature and heavy metal exposure can affect/impair aerobic energy metabolism in aquatic ectotherms.

3.1. Energy demand

The effects of elevated temperature on the metabolic rate and energy demand of aquatic ectotherms has been extensively studied and summarized in excellent reviews (Pörtner 2001, 2002, Hochachka & Somero 2002 and references therein). Within the thermal tolerance range, a rise in temperature results in a proportional increase in different aspects of the standard metabolic rate, including costs of protein synthesis, ATP turnover, mitochondrial proton leak and non-mitochondrial respiration (Cherkasov et al. 2006a). Beyond the tolerance range at the pejus and upper critical temperatures, some cellular maintenance costs (especially costs of mitochondrial maintenance due to the proton leak) may increase disproportionately at the expense of other cellular functions (Pörtner 2001).

Exposure to toxic metals may also result in an increased basal metabolic demand (i.e. the amount of metabolic energy required for the basal maintenance and survival of the individual) (Sibly & Calow 1989, Calow & Forbes 1998); however, unlike temperature, metal exposures typically lead to a disproportionate increase in the aspects of cell metabolism responsible for cellular detoxification and repair (Sibly & Calow 1989, Calow & Forbes 1998, Cherkasov et al. 2006a, Ivanina et al. 2008a). Our studies showed that both protein synthesis rate and oxygen consumption required to cover the costs of protein synthesis increased in eastern oysters *Crassostrea virginica* exposed to Cd (Cherkasov et al. 2006a, Ivanina et al. 2008a). An increase in the cellular protein synthesis in metal-exposed oysters was associated with an elevated expression of cellular protection proteins, such as metallothioneins, P-glycoproteins and heat shock proteins (Ivanina & Sokolova 2008, Ivanina et al. 2008a). Similarly, yellow perch *Perca flavescens* from metal-contaminated lakes had significantly higher liver biosynthetic capacity (as shown by elevated activity of nucleotide diphosphate kinase), indicating that elevated protein synthesis is involved in the protective response against metals in the field (Couture & Kumar 2003). Induction of metallothioneins

is a hallmark response to metal exposure (Bauman et al. 1993, Roesijadi 1996), and heat shock proteins (HSP) are also commonly up-regulated in metal-exposed animals (reviewed by Feder & Hoffman 1999). Elevated synthesis of cellular protection proteins may contribute to elevated standard metabolic rates and maintenance costs in metal-exposed ectotherms. According to some estimates, stress proteins can represent up to 7% of the total protein pool with increasing contribution during stressful conditions (Kultz 2003), and the synthesis rate of HSPs is comparable to some housekeeping genes such as actin, even under non-stress conditions (Lanks 1983). Metallothionein synthesis may account for up to 5% of the total metabolic rate in metal-challenged organisms (Barber et al. 1990). Given that total protein synthesis typically accounts for 10 to 20% of the standard metabolic rate (Hand & Hardewig 1996, Cherkasov et al. 2006a), metallothionein and HSP synthesis may represent a significant additional cost to the organism, diverting energy from essential functions such as growth, reproduction and immunity toward metal detoxification and damage repair.

Other protective mechanisms, such as glutathione expression, antioxidants, or cellular repair mechanisms, may also contribute to the elevated maintenance costs in metal-exposed organisms. Elevated glutathione expression is a common response to low (sublethal) metal levels (Viarengo et al. 1990, Ringwood et al. 1999, Mitchelmore et al. 2003, Regoli et al. 2004, Lannig et al. 2006) and has been proposed to aid detoxification by binding the toxic free ion form of metals, although at high metal levels this response may be impaired and gluthathione depletion ensues (Regoli & Principato 1995, Ringwood et al. 1998, Mitchelmore et al. 2003, Toplan et al. 2003). Notably, our studies show that temperature can affect this response in aquatic ectotherms; thus, glutathione levels increased in oysters during long-term Cd exposure at 20 and 24°C, but not at 28°C, indicating that this protective response was impaired at elevated temperatures (Lannig et al. 2006). The expression of mitochondrial Lon protease, a multifunctional enzyme that degrades damaged proteins and naturally short-lived proteins, was also up-regulated in Cd-stressed oysters, indicating higher protein turnover in their mitochondria, possibly to degrade Cd-damaged proteins (Sanni et al. 2007). Interestingly, Lon protease expression tended to be lower in 28°C-acclimated oysters than in 12°C- or 20°C-acclimated ones (Sanni et al. 2007), suggesting that elevated temperature can negatively affect protein quality control systems in oyster mitochondria, contributing to the above-described decline in mitochondrial capacity in Cd- and heat-stressed oysters. Overall, the interactive effects of temperature and metal stress on antioxidants and cellular repair mechanisms have not been extensively studied

in ectotherms and require further investigation to determine whether similar limitations of protective response at high temperatures apply.

High energy demand in metal-exposed aquatic ectotherms is further supported by depletion of body energy stores during metal exposures, especially when combined with elevated temperatures. Thus, in oysters *Crassostrea virginica*, simultaneous exposure to elevated temperatures and Cd resulted in a significant depletion of glycogen stores, whereas each of these 2 stressors alone had no effect on tissue glycogen content (Lannig & Sokolova unpubl. data). Depletion of body glycogen and/or lipid reserves was also observed in fishes (sea bass *Dicentrarchus labrax* and rainbow trout *Oncorhynchus mykiss*), gastropods (dogwhelk *Nucella lapillus*) and crustaceans (crabs *Scylla serrata* and the harpacticoid *Tigriopus japonicus*) exposed to Cd, Cu and/or tributyltin (TBT) (Reddy & Bhagya-

lakshmi 1994, Cattani et al. 1996, Clearwater et al. 2002, Kwok & Leung 2005). At high concentrations of Cu and TBT, *T. japonicus* entered a metabolically dormant state enhancing their survival (Kwok & Leung 2005), showing that an ability to channel energy into coping with toxins (even at the expense of other biological functions) may be essential in survival of metal exposures.

It is worth noting that the literature on the effects of metals on metabolic rates in aquatic ectotherms reveals a complicated and seemingly controversial picture with the rates of metabolism increasing, decreasing, or not changing in metal-exposed organisms (see Table 4 and text below for references). In general, the degree and direction of metal effects on aerobic metabolism (measured as the rate of oxygen consumption) depend on the metal, its concentration and exposure regime (acute or chronic). Typically, chronic ex-

Table 4. Effects of metals on aerobic metabolic rates in aquatic ectotherms. Metal effects—positive: metabolic rates increase in metal-exposed organisms; negative: metabolic rates decrease in metal-exposed organisms; none: metabolic rates do not change in metal-exposed organisms. $\dot{M}O_2$ defines whether standard (reflecting energy demand for basal maintenance), routine (energy demand for basal maintenance plus costs of non-quantified routine activity), active (energy demand for basal maintenance plus costs of maximum aerobic performance) metabolic rates were determined in a particular study. Question mark (?) indicates that the metabolic rate could not be classified as standard, routine, or active due to insufficient data presented in this paper. Article search was performed in Web of Science and PubMed databases using keywords 'metal' ('metabolic rate' or 'oxygen consumption'); only articles discussing aerobic metabolism in aquatic ectotherms were selected

	Species	Metal	$\dot{M}O_2$	Metal effect	Source
Vertebrates					
Fishes	*Salmo gairdneri*	Cu	Active	Negative	Waiwood & Beamish (1978)
	Perca flavescens	Cu, Cd	Post-active[a]	Negative	Couture & Kumar (2003)
	Cyprinus carpio	Cd	Routine	Negative[b] Positive[c]	Suresh et al. (1993)
Invertebrates					
Crustacea	*Orconectes immunis*	Cu	Routine	Positive[d], Negative[e]	Khan et al. (2006)
		Cd, Zn, Pb	Routine	Negative[f]	Khan et al. (2006)
	Callinectes similis	Chromium (Cr)	Routine	Negative	Ramirez et al. (1989)
		Cd	Routine	Positive[g] None[h]	Ramirez et al. (1989)
	Cherax destructor	Lead (Pb)	Routine	Negative	Ahern & Morris (1999)
	Palaemon elegans	Cd, Cr	?	Positive	Moraitou-Apostoloupoulou et al. (1982)
	Tisbe holothuriae	Cu	?	Positive	Moraitou-Apostoloupoulou et al. (1983)
	Acartia clausa	Cu, Cd, Cr	?	Positive	Moraitou-& Verriopoulos (1979)
	Farfantepenaeus paulensis	Cu, Zn	?	Negative	Santos et al. (2000)
Mollusks	*Crassostrea virginica*	Cd	Standard	Positive	Lannig et al. (2006)
	Ruditapes decussatus	Cd	Standard	Positive	Baghdiguian & Riva (1985)
	Hemifusus tuba	Arsenic	Routine	None	Depledge & Phillips '(1987)
	Perna viridis	Cr, silver (Ag)	Routine	Negative	Vijayavel et al. '(2007)

[a]Proxy for maximal sustainable $\dot{M}O_2$; [b]at lethal [Cd] levels; [c]at sublethal [Cd] levels; [d]20°C; [e]23–27°C; [f]20–27°C; [g]at 4 mg Cd l⁻¹; [h]at [Cd] < and >4 mg Cd l⁻¹

posures to low (environmentally relevant) metal levels either do not affect respiration rate of aquatic organisms or result in elevated rates of oxygen uptake (Moraitou-Apostolopoulou & Verriopoulos 1979, Moraitou-Apostolopoulou et al. 1982, Baghdiguian & Riva 1985, Ramirez et al. 1989, Lannig et al. 2006 and references therein). In contrast, acute exposures to high metal concentrations usually lead to a decline in the rates of oxygen uptake (Abdullah & Ireland 1986, Ramirez et al. 1989, Spicer & Weber 1991, Cheung & Wong 1998, Leung et al. 2000, Rao & Khan 2000 and references therein). Generalizations of the metabolic effect of metals and temperature–metal interactions are further complicated by the current lack of a standardized approach to $\dot{M}O_2$ determination in toxicological studies of aquatic ectotherms. Indeed, different studies measured the effects of metal exposure on standard metabolic rates, routine metabolic rates, or active metabolic rates, each of which would predictably respond differently to metal exposure and temperature stress. While metal exposure is expected to elevate the rates of standard (basal) metabolism due to higher maintenance costs for detoxification and damage repair, its effects on routine metabolic rate (which in addition to maintenance costs includes varying and usually non-quantified amounts of routine activity, such as locomotion, specific dynamic action due to food digestion, etc.) or active metabolic rate may be different. In fact, if the energy demands for basal maintenance are very high, one would anticipate a decrease in other activities such as locomotion, reproduction, etc.; if these decreases balance the increase in standard metabolic rate, no change in the total $\dot{M}O_2$ will be found, and, if the drop in these activities is larger, a decline in $\dot{M}O_2$ will be seen.

Overall, the routine metabolic rate is probably the least useful (and paradoxically most often measured) parameter for determining the effects of metal exposure on energy costs, because varying levels of routine activities will mask the effects of metal exposure, a fact demonstrated by the great variability of response to metals when routine $\dot{M}O_2$ are measured (Table 4). In contrast, standard metabolic rates and active metabolic rates are easier to interpret from the viewpoint of physiology (reflecting basal maintenance costs and maximum aerobic capacity, respectively) and show a more consistent response to metal exposure (Table 4 and text below). The few currently available studies that have specifically measured standard metabolic rates (SMR) in response to metals in aquatic ectotherms support the hypothesis that exposure to sublethal metal concentrations result in elevated SMR (Table 4). Thus, SMR was considerably elevated in Cd-exposed eastern oysters (Cherkasov et al. 2006a, Lannig et al. 2006) and in Cd-exposed marine clams *Ruditapes decussatus*

starved for 2 mo (Baghdiguian & Riva 1985). Notably, Cd exposure also resulted in a stronger negative tissue growth in starved clams and inverted the order in which different energy reserves were used during starvation (Baghdiguian & Riva 1985). In control animals, lipoprotein reserves were used first, followed by carbohydrates (after 1 mo) and proteins (after 2 mo), while, in Cd-exposed animals, carbohydrate reserves were used up first, followed by lipoproteins and lastly proteins (Baghdiguian & Riva 1985). This order of use of energy reserves closely resembles that used during gonadal maturation and suggests that Cd exposure leads to an additional energy expenditure that requires reserves that can be rapidly mobilized, such as glycogen.

In contrast, the active metabolic rate (measured as the maximum sustainable $\dot{M}O_2$) decreased in steelhead trout *Salmo gairdneri* following 5 d of Cu exposure, implying problems with oxygen uptake and/or delivery during active locomotion (Waiwood & Beamish 1978). Post-exercise $\dot{M}O_2$ after swimming to exhaustion (which is a proxy for maximal sustainable $\dot{M}O_2$) decreased in yellow perch *Perca flavescens* from metal-contaminated lakes and was negatively related to Cu and Cd levels in the fish (Couture & Kumar 2003). Aerobic swimming performance, as determined by the maximal swimming speed (U_{crit}) and relative scope for activity, was also impaired in perch with high accumulated levels of Cu and Cd from polluted lakes (Rajotte & Couture 2002, Couture & Kumar 2003). Similarly, in Cu-exposed rainbow trout *Oncorhyncus mykiss* a strong reduction in swimming performance was observed, which progressed as the duration of Cu exposure increased (Clearwater et al. 2002). This indicates similarity of aerobic response to metals in laboratory and field exposures. A decrease in the active metabolic rate in metal-exposed ectotherms may reflect an impaired capacity for aerobic ATP production and systemic oxygen delivery (Byczkowski & Sorenson 1984, Wallace & Starkov 2000, Sokolova 2004, Ivanina et al. 2008b, Lannig et al. 2008) and/or an energetic trade-off due to the metal-induced increase of basal maintenance costs (Sibly & Calow 1989, Calow & Forbes 1998, Cherkasov et al. 2006a, Lannig et al. 2006) and, as a result, less energy available for sustained activity. Irrespective of the exact mechanisms, a decrease in active metabolic rate may negatively affect the organism's locomotion and have an impact on its ability to catch prey or avoid predators.

The above data show that the hypothesis that elevated energy demand for basal maintenance plays a key role in the interactive effects of temperature and metal stress is both theoretically plausible and experimentally supported by the available (albeit limited) data. Carefully designed studies are needed to extensively test this hypothesis. Several complementary

approaches can be used to assess the metabolic costs of metal exposure and their interactions with elevated temperatures. Optimally, all components of energy budget (including standard metabolic rate, as well as scopes for growth, reproduction and activity) should be determined to identify the critical costs of metal and temperature stress. However, such an approach is time- and effort-consuming and may not be feasible for all organisms and practical applications. Alternatively, SMR can be determined in post-prandial resting animals with no locomotory activity; if metal detoxification and damage repair is associated with a significant energy cost, an increase in SMR is expected. Determination of metabolic rate with simultaneous quantification of the activity levels (i.e. using swimming tunnels or simultaneous $\dot{M}O_2$ measurements and video recording) can also provide important information of energy costs for metal and temperature stress by comparing whether slopes of $\dot{M}O_2$ on activity levels and/or maximal sustained $\dot{M}O_2$ and SMR (extrapolated as $\dot{M}O_2$ at zero activity) are affected by these 2 stressors. Determination of routine metabolic rates without the simultaneous quantification of activity levels cannot be recommended, because the interpretation of such data would be hindered by the impossibility to separate the potentially opposing effects of metal exposure and/or temperature on the basal maintenance costs and on the costs of active locomotion.

3.2. Energy supply

An elevated energy demand for basal metabolism appears to be a common mechanism of action for trace metals and elevated temperature stress, which may account for their synergistic effects on animal physiology and survival. However, elevated energy demand *per se* may not be a problem as long as it is met by a sufficient energy supply from food and/or body energy resources and as long as the systemic functions (ventilation and circulation) and cellular metabolic machinery can provide enough ATP to sustain elevated basal metabolism. The existing data, however, indicate that this is not the case. For example, in eastern oysters *Crassostrea virginica*, elevated temperature exaggerates the effects of a toxic metal (Cd) by further increasing standard metabolic rate until, at a certain threshold of combined temperature and metal stress, no further increase in oxygen uptake is possible due to limitations of oxygen uptake systems (Lannig et al. 2006). As a result, blood oxygenation decreases in oysters exposed to Cd at 28°C, but not at 20 or 24°C (Lannig et al. 2008). In oysters, circulatory system capacity, including heart rate and tissue hemolymph supply, was similar between control and Cd-exposed animals even at high temperatures (Lannig et al. 2008), in-

dicating a depressed capacity for adjustments in circulatory performance to counteract the concomitant limitation of oxygen uptake in metal-exposed animals (Brown & Newell 1972, Spicer & Weber 1991, Nonnotte et al. 1993, Lawson et al. 1995, Hebel et al. 1997, Gregory et al. 1999, Leung et al. 2000). Indeed, high levels of trace metals often suppress ventilation and perfusion of respiratory organs in aquatic ectotherms, although relatively little is known about their effects at low sublethal concentrations. An important mechanism for such suppression involves damage to respiratory epithelia, impairing oxygen uptake and leading to hypoxemia. Thus, exposures to high levels of Cd, Cu, Zn, or Hg result in degeneration of cilia, vacuolization, cellular hyperplasia and the appearance of necrotic cells in gills of marine mollusks and crustaceans (Brown & Newell 1972, Spicer & Weber 1991, Nonnotte et al. 1993, Lawson et al. 1995, Hebel et al. 1997, Gregory et al. 1999, Leung et al. 2000). Excessive mucus production is another common response to acute metal stress, limiting absorption of metals on the one hand, but interfering with O_2 uptake on the other (Naimo et al. 1992, Sze & Lee 1995, Leung et al. 2000). In some organisms (such as the crab *Callinectes similis*) exposure to Cd and Cr resulted in a reduction in the percentage of oxygen extraction (calculated as a ratio of $\dot{M}O_2$ to the initial O_2 concentration in respiration chambers), indicating a lower efficiency of O_2 uptake at the respiratory surfaces (Ramirez et al. 1989). Similarly, exposure to 0.5 or 100 mg l^{-1} Pb resulted in a notable reduction of oxygen transfer across the gills in crayfish *Cherax destructor* (Ahern & Morris 1999). Combination with elevated temperature would further exaggerate this hypoxemia due to the elevated oxygen demand on the one hand, and lower O_2 solubility at high temperatures on the other.

The effects of trace metal exposure on the circulation system in aquatic ectotherms have not been extensively studied, and available data indicate variable responses. In oysters, heart rate was not affected by exposure to Cd in the environmentally relevant temperature range (20 to 28°C) (Lannig et al. 2008). In contrast, in the crab *Carcinus maenas*, acute exposure to high Cu levels resulted in a decrease of heart rate (Depledge 1984). In the marine gastropod *Hemifusus tuba* exposure to arsenic led to a strong decrease in heart rate at 30°C, but no change at 23.5°C (Depledge & Phillips 1987). Notably, arsenic exposure resulted in a lowered sensitivity to temperature in *H. tuba* (Q_{10} for heart rate was 1.51 in As-exposed snails vs. 2.08 in the controls), indicating that circulation may become limiting in metal-exposed animals at elevated temperatures (Depledge & Phillips 1987).

Oxygen transport is another aspect of aerobic metabolism that can be impaired by metal exposure and elevated temperatures. In species that utilize hemocyanin

or hemoglobin for oxygen transport, heavy metals can disrupt the respiratory functions of these pigments, negatively affecting the oxygen-carrying capacity of the blood. Thus, in dogwhelks *Nucella lapillus*, the O_2-carrying capacity of hemolymph was significantly reduced by Cd exposure (Leung et al. 2000), and Cu exposure resulted in a decrease in hemocyanin concentration in the hemolymph of *Carcinus maenas* (Bjerregaard & Vislie 1986). In the polychaete *Arenicola marina*, Cu and Zn exposure resulted in a decrease of oxygen affinity of their respiratory pigment erythrocruorin, and thus inhibition of O_2 binding at the respiratory surface and O_2 delivery to metabolizing tissues (Everaarts et al. 1979, Everaarts 1986). Similarly, Cd exposure led to a decrease in oxygen affinity of erythrocruorin in *A. marina*, although this effect was only evident *in vivo* and not *in vitro* (Everaarts & Reichert 1988). Cd exposure also considerably increased the apparent heat of oxygenation of erythrocruorin, which would diminish the adaptational capacity of the respiratory function of *A. marina* toward temperature changes in its natural habitat (Everaarts & Reichert 1988). In arcid bivalves *Scapharca inaequivalvis*, blood oxygen transport mediated by hemoglobin-containing erythrocytes is also impaired by Cd exposure, although in this case the mechanism involves a decrease in hematocrit and hemocyte count, and not in oxygen affinity (Weber et al. 1990). Given that the oxygen affinity of respiratory pigments, including hemoglobins and hemocyanins, tends to decrease with increasing temperatures (Burnett 1992, Weber & Vinogradov 2001, Decker et al. 2007), the combined action of trace metals, high temperature and low oxygen solubility in the water may strongly limit oxygen uptake and delivery in the respiratory organs of aquatic ectotherms.

Temperature and metal exposure can also synergistically affect energy supply at the cellular ATP production sites. Trace metals strongly affect mitochondrial function by reducing activity of the electron transport chain and ATP production, decreasing mitochondrial efficiency, elevating mitochondrial reactive oxygen species (ROS) production and/or increasing mitochondrial maintenance costs through elevated proton leak (Wallace & Starkov 2000, Sokolova 2004, Cherkasov et al. 2006b and references therein). Studies in our laboratory have shown that elevated temperatures strongly increase the sensitivity of mitochondria to toxic metals. Thus, apparent inhibition constants for Cd (reflecting Cd concentrations required to inhibit 50% of respiration) were reduced by nearly 2 orders of magnitude by a temperature increase from 15 to 35°C in oyster mitochondria: from 80 to 3 µM for ADP-stimulated State 3 respiration and from 172 to 2 µM for resting (State 4) respiration, respectively (Sokolova 2004). Moreover, exposure to Cd resulted in a significant decrease in mitochondrial abun-

dance in gill and hepatopancreas (digestive gland) of oysters, with a notably stronger reduction at 28°C than at 20 or 12°C (Cherkasov et al. 2006a). Elevated temperatures also exaggerated the Cd-induced inactivation of the key mitochondrial enzyme aconitase (Cherkasov et al. 2006b) and inhibition of electron transport complexes and Krebs cycle enzymes in oyster mitochondria (Ivanina et al. 2008b). Activation energy of several key mitochondrial enzymes was also significantly reduced by Cd exposure, suggesting that their ability to adequately respond to changes in environmental temperature is impaired (Ivanina et al. 2008b). This implies that aerobic capacity can be strongly impaired by the combined action of elevated temperature and trace metals in ectotherms, resulting in an energy deficiency even when the systemic oxygen supply is unaffected.

Last but not least, both high temperature and metal exposure can result in oxidative stress due to the excessive ROS production in mitochondria, inhibition of cellular antioxidant defense, or both. Oxidative stress, in turn, results in damage to the vital cellular components, including membranes, proteins and DNA, and eventually leads to cell death. The effects of temperature and trace metals as single stressors on oxidative stress have been extensively studied, and there are several excellent reviews dealing with these issues, to which we refer the interested reader (Valko et al. 2005, Abele et al. 2007 and references therein). In contrast, very few studies have addressed the combined effects of these 2 stressors on oxidative stress, and the mechanisms and physiological consequences of their interaction on ROS production and antioxidant defense is poorly understood. Studies in our laboratory have shown that exposure to Cd results in oxidative damage of oyster tissues at 28°C, but not at 20 or 24°C, as indicated by accumulation of malondialdehyde, an end product of lipid peroxidation (Lannig et al. 2006). This suggests that at elevated temperatures, tissue antioxidant defenses are overwhelmed by excessive Cd-induced ROS production, and oxidative damage ensues. This view is further supported by the fact that ROS-mediated inactivation of mitochondrial aconitase in oyster mitochondria was significant at 30°C, but not at 20°C (Cherkasov et al. 2006b). Further studies are needed to determine whether temperature–metal synergy on ROS production is a general phenomenon in aquatic ectotherms, and what implications this has for whole-organism physiology and survival.

4. EFFECTS OF METALS ON THERMAL TOLERANCE

The interactive effects of elevated temperature and trace metal exposure have 2 consequences in aquatic

ectotherms: (1) the above-described sensitization of an organism to metal toxicity and (2) a decrease in thermal tolerance limits in metal-exposed animals. These consequences are, in fact, 2 sides of the same coin and are tightly linked with the synergistic effects of temperature and metal stress on aerobic metabolism.

According to the concept of oxygen-limited thermal tolerance in aquatic ectotherms (Pörtner 2001), the temperature range in which an animal exhibits highest capacity for growth and reproduction is determined by its optimized oxygen supply. Upper and lower limits of thermal tolerance are set by limitations in aerobic scope, due to the onset of a mismatch between oxygen supply and demand and a reduced capacity to deliver oxygen to the tissues/organs (see Frederich & Pörtner 2000, Mark et al. 2002, Wilson et al. 2002, Sartoris et al. 2003, Lannig et al. 2004, 2008, Pörtner et al. 2006 and references therein). This limitation in aerobic scope arises before thermal stress causes a transition to anaerobic metabolism and further effects at cellular and biochemical levels when critical temperatures are reached (Pörtner 2002, Pörtner & Knust 2007). In addition to impaired circulatory and ventilatory performance, other factors such as mitochondrial functioning and oxygen-carrying capacities by respiratory pigments contribute to thermally induced limitation of oxygen (Melzner et al. 2007). The width of the window of thermal tolerance may vary greatly between species and environments and is typically narrow in stenothermal species from permanently cold environments (e.g. deep sea and polar regions) and the tropics, and considerably wider in eurythermal temperate species, especially those from habitats with wide temperature fluctuations, such as intertidal zones and shallow waters (Somero & de Vries 1967, Pörtner et al. 1999, 2001, 2007, Sommer & Pörtner 2002, Peck et al. 2004, Somero 2005, Compton et al. 2007).

The above-described effects of metal exposure on metabolism and the observed relationship between temperature tolerance and aerobic metabolism tally well with the following assumption: metal exposure will interfere with thermal tolerance, resulting in decreased temperature limits in metal-exposed animals (Fig. 3), especially in light of recent findings that show that exposure to toxic metals results in hypoxemia in aquatic ectotherms (e.g. in the carp *Cyprinus carpio* exposure to Cd led to the onset of partial anaerobiosis, as indicated by the upregulation of lactate dehydrogenase activity and significant accumulation of the anaerobic metabolites pyruvate and lactate; Suresh et al. 1993). Notably, transition to partial anaerobiosis was detected at both low (sublethal) and lethal Cd levels, although putative mechanisms for this transition were different: at lethal Cd levels it was associated with inhibition of aerobic respiration due to gill
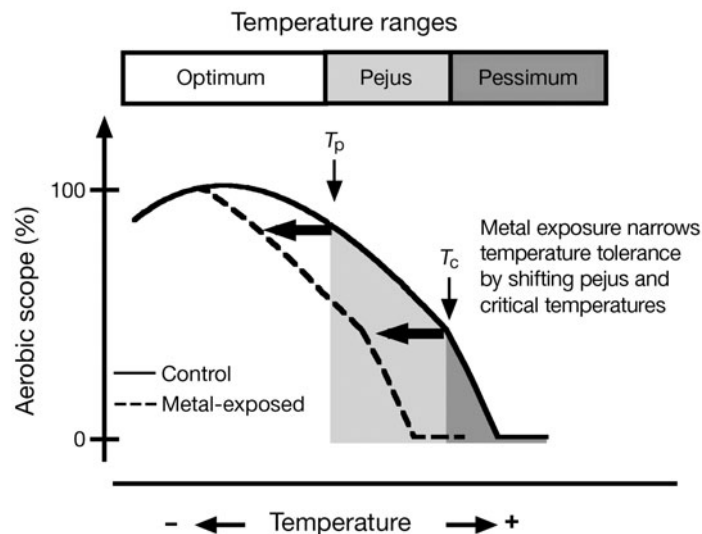

Fig. 3. Effects of metal exposure on thermal tolerance of aquatic ectotherms. Interpretation of pollution effects on thermal tolerance limits in the framework of the conceptual model of oxygen-limited thermal tolerance in water-breathing animals (modified after Frederich & Pörtner 2000, see also Pörtner 2001). Following Shelford's law of tolerance, the concept defines the temperature tolerance thresholds pejus (T_p) and critical (T_c) temperatures. The pejus range is characterized by a declining aerobic scope and extends until anaerobic metabolism finally sets in (T_c) caused by temperature-induced reduction in aerobic scope due to a mismatch between oxygen demand and supply capacities (see Section 4). Metal exposure impairs aerobic capacities, causing a downward shift of T_p and T_c temperatures as indicated by the bold arrows

damage, whereas at sublethal Cd exposures anaerobic metabolism occurred hand-in-hand with high aerobic oxidation and probably reflected limitation of aerobic metabolism and its failure to fully cover elevated energy demand due to cellular detoxification and repair (Suresh et al. 1993). A similar situation was observed in crabs *Scylla serrata* during Cd exposure, which resulted in impaired mitochondrial enzyme capacities and the onset of partial anaerobiosis with induction of glucose-6-phosphate dehydrogenase and lactate accumulation (Reddy & Bhagyalakshmi 1994). A compensatory increase in tissue anaerobic capacities that went hand-in-hand with a decrease in aerobic scope was also found in metal-contaminated yellow perch *Perca flavescens* and Mozambique tilapia *Oreochromis mossambicus* (James et al. 1992, Couture & Kumar 2003, Couture & Rajotte 2003). This implies that metal stress combined with elevated temperatures will result in a rapid onset of tissue hypoxemia and aerobic energy deficiency, shifting pejus and critical temperatures to the lower values (Fig. 3).

Although the effects of metal exposure on critical and pejus temperatures have not been specifically studied, several studies provide evidence that expo-

sure to metals can indeed affect thermal tolerance of aquatic ectotherms. Thus, the critical thermal maximum (CT_{max}; determined as the temperature at which coordinated locomotion of an organism is disrupted, indicating neural dysfunction) was reduced by exposure to Cd or Cr in the marine prawn *Macrobrachium rosenbergii* and in the stonefly nymph *Clioperla clio* (Poulton et al. 1989, Rosas & Ramirez 1993). The decrease in CT_{max} was accompanied by a decrease in tissue O_2 concentrations in the prawn, indicating that disruption of energy metabolism was involved (Rosas & Ramirez 1993). In coho salmon *Oncorhynchus kisutch* and steelhead trout *Salmo gairdneri* exposure to Ni also led to a reduction in CT_{max} and the upper lethal temperature limit, and CT_{max} values of Ni-exposed fish were also more heterogeneous than in the controls (Becker & Wolford 1980). A similar decrease in CT_{max} was found in muskellunge fry *Esox masquinongy* exposed to sublethal concentrations of arsenic (Paladino & Spotila 1978). In contrast, Cd exposure of green sunfish *Lepomis cyanellus* had no effect on CT_{max}, perhaps due to the fact that the green sunfish is a very hardy eurythermal species with a high thermal tolerance (Carrier & Beitinger 1988).

In active organisms such as fishes, metal exposure can lead to behavioral selection of a lower preferred temperature (if given a choice) (Gordon 2005). Thus, Cd and Cu exposure resulted in a decrease in the selected water temperature in Atlantic salmon *Salmo salar*, whereas Zn had no effect (Peterson 1976, cited according to Gordon 2005). Interestingly, respiratory poisons and metabolic uncouplers have the same effect on preferred temperatures, suggesting that interference with aerobic metabolism underlies these effects. Thus, the mitochondrial uncoupler pentachlorophenol and an inhibitor of cytochrome *c* oxidase, potassium cyanide, decreased preferred temperature in *S. salar*, although 2,4-dinitrophenol had no effect on preferred temperature, despite uncoupling of mitochondria (Javaid 1972, Peterson 1976). In the toad *Buffo marinus*, injections of sodium azide or cyanide also led to a behavioral selection of a lower preferred temperature (Branco & Malvin 1996), as did exposure of protozoans *Paramecium caudatum* to sodium azide, cyanide, or 2,4-dinitrophenol (Malvin et al. 1994, Malvin 1998).

As a corollary, heavy metal exposure will have deleterious effects on the metabolic physiology of ectotherms, limit-

ing their tolerance to elevated temperatures (e.g. during seasonal warming or global climate change). Here, we propose a conceptual model (Fig. 4) that integrates different aspects of metal toxicity under the umbrella of energy metabolism and bioenergetics; according to this model, metal exposure interferes with cellular processes such as ion homeostasis, protein stability and mitochondrial efficiency, leading to elevated costs for maintenance and detoxification (Fig. 4). Moreover, metal-induced effects on mitochondrial capacities and damage of gill structure and/or cardiac function impair oxygen supply systems. These opposing effects are generally balanced at moderate temperatures so that detoxification and repair capacities are sufficiently high to minimize the negative effect of metal exposure on oxygen supply systems (depending on metal concentration), and vice versa the oxygen supply is sufficiently high to cover elevated maintenance costs. The metabolic effects of metals become critical once an organism is in its thermal pejus range, where the aerobic scope is limited. With rising temperature, the synergistic effects of elevated temperature and metal exposure on energy demand for basal maintenance, detoxification and damage repair override the aerobic
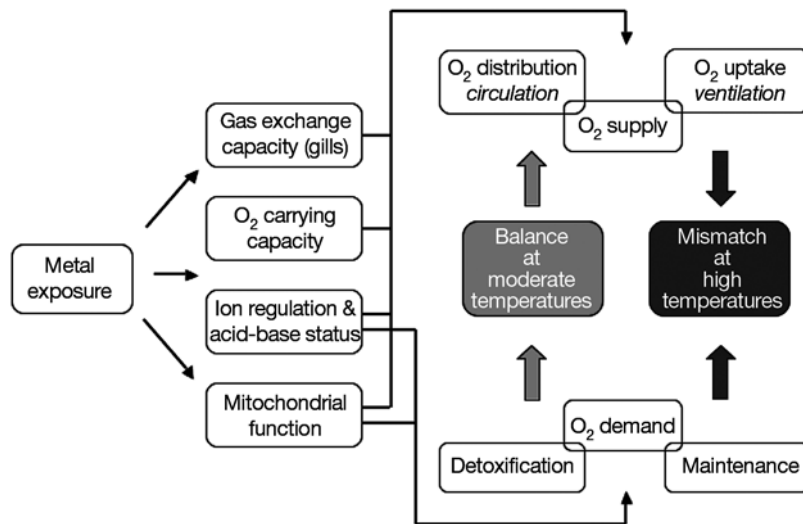

Fig. 4. Generalized physiological model of interactive effects of temperature and trace metals on aquatic ectotherms. Metal exposure interferes with several physiological and biochemical processes that affect aerobic metabolic capacities. At moderate temperatures, the metal-induced rise in oxygen demand can be balanced by a corresponding rise in oxygen supply. At elevated temperatures these effects become detrimental, resulting in a mismatch between oxygen demand and supply mainly due to impaired ventilatory performance (see Sections 3.2 and 4 for details). This model does not cover cases of metabolic rate depression, where acclimation/adaptation to metal exposure occurs by decreasing the rates of metabolic processes and entering a metabolically depressed or dormant state with a concomitant decrease in energy demand and supply. According to the available literature, such situations are rare in metal- and temperature-stressed ectotherms

metabolic machinery, resulting in progressive hypoxemia. As a result of the mismatch between elevated energy demand and limited energy supply during exposures to elevated temperatures and metal, energy-dependent cellular protective mechanisms involved in detoxification and damage repair (e.g. metallothioneins and HSPs) are more likely to fail, leading to elevated mortality and whole-organism physiological stress (Lannig et al. 2006, 2008).

5. SUMMARY AND FUTURE DIRECTIONS

Interactions between environmental temperature and metal pollution strongly affect physiological tolerance to both stressors and can limit the survival and distribution of ectotherm populations in the face of global climate change and increasing anthropogenic pollution of aquatic environments. Interference with aerobic metabolism, including energy demand, oxygen supply and mitochondrial function, forms a physiological basis for these interactions. Both elevated temperature and toxic metal stress can, independently of each other, result in elevated maintenance costs, reduce mitochondrial efficiency and impair oxygen uptake and delivery to the tissues, leading to hypoxemia and energy deficiency. As a result, exposure to one of these stressors sensitizes an organism to the other. This finding may have broader implications and holds true not only for trace metals, but also for other pollutants and environmental stressors that require an elevated energy demand for stress or negatively affect energy supply or both, such as hypoxia, metabolic toxin, antiparasite and other immune defense mechanisms (Malvin et al. 1994, Branco & Malvin 1996, Stefaniak et al. 2005, Flye-Sante-Marie et al. 2007). In the future, detailed studies focusing on energy budget as a key target for multiple stressors will be needed to extensively test this bioenergetic hypothesis of severe temperature–pollutant interactions on aerobic energy metabolism of marine ectotherms and to extend it to other pollutants and natural stressors. Currently, very little is known about the effects of multiple stressors, such as salinity, hypoxia, food availability or — against the background of climate change — such as ocean acidification and increased CO_2 levels, on the sensitivity to temperature and metals; however, recent studies indicate that multiple stressors in the field may increase sensitivity to metals in aquatic ectotherms when compared to laboratory exposures at the same temperatures and metal concentrations (Witeska & Jezierska 2003, Gauthier et al. 2006). Another important, but currently understudied, aspect of temperature–pollution interaction is an understanding of the effects of fluctuating (as opposed to constantly elevated) temperatures or long-term temperature acclimation/adaptation, which may affect organisms differently than acute temperature change (Spurgeon et al. 2005). Using these studies, quantitative toxicokinetic and physiological models of temperature–pollution interactions can be developed that will assist in predicting the effects of pollutants on ectotherm populations in the face of global climate change. Physiological studies of temperature–pollution interactions at all levels of biological organization (from molecular/cellular to whole organism and populations) would be crucial for generalizations and predictions of the effects of stressors within and across species. Since the relationships become more and more complicated as the number of variables increases, computer models will be critical for fully exploring these relationships. Such models will become indispensable for predicting the effects of multiple stressors on ectotherm populations facing global climate changes and determining safety margins in ecological risk assessments, and physiological studies will play a key part in such models by providing realistic input values for model parameters.

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