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Perspective

Redox Metabolism in Fishes Under Thermal Stress Warrants More Attention

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Abstract: Any process that maintains the redox environment in aerobes is defined as redox homeostasis. Redox homeostasis is disturbed in favor of a prognostic situation either due to increase in generation of reactive oxygen species (ROS) or due to collapse of cellular antioxidant defenses. Both conditions are greatly affected by environmental factors, and thereby, manipulate physiology of aerobes. Rise in aquatic habitat temperature induces oxidative stress in fish as a consequence of accelerated generation of ROS as by-products of elevated metabolic activities. Reactive oxygen species, if not neutralized, oxidize biomolecules present in their vicinity and impairs their biological properties and, thereby, cellular physiology. The phenomenon is referred as "oxidative stress". Augmentation of oxidative stress is linked to various pathophysiological states reported for aerobes. Also elevation in temperature of marine or brackish water bodies results in augmentation of salinity which in turn induces oxidative stress in fish and other aquatic fauna. This may have dire consequences on fish by accelerating aging phenomenon as oxidative stress and aging are interrelated processes. Thus, it can be predicted that exposure to short intense or long gradual rise in aquatic habitat temperature due to global warming may trigger oxidative stress in aquatic fauna including fish which may affect their growth pattern, reproductive capacity, survivability and finally longevity. Fish are one of the major components of global ecosystem. Any imbalance in fish population will not only affect aquatic ecosystem but also may have dire long term consequences on global food chain. Therefore, more research must be focused not only to understand the physiological aspects related to oxidative stress in context to thermal stress for better health status in fish but also to develop new strategies for fish endurance it as thermal stress is imminent outcome of global warming.

Keywords: Habitat warming, Fish physiology, Fish growth, Oxidative metabolism, Thermal stress

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Introduction

Fish belong to a paraphyletic group of organisms that consist of all gill-bearing aquatic craniates that lack limbs with digits. Fish as the major group of poikilotherms can be considered as the principal targets under rise in acute or gradual temperature of their natural habitat because these organisms lack proper physiological mechanism(s) to regulate their internal body heat in relation to changing environmental temperature (Carey and Lawson, 1973; Goldman, 1997). Consequently, their energy metabolism may be affected by increasing environmental temperature as observed in other poikilotherms (Galli and Rechards, 2012). It may result in increase in production of reactive oxygen species (ROS) either due to elevated metabolism or due to collapse of antioxidant defences, or both, which in turn may induce oxidative stress (OS) in fish by impairing functions of biomolecules as a consequence of their oxidation. Os is reported to be associated with various physiological aspects of aerobes such as growth, development and aging. Fish exhibit a great diversity in ecology and serve as a vital component in aquatic ecosystem. Also it is an important trophic level in global food chain. Therefore, increase in habitat temperature due to global warming may induce OS in fish and may hamper their growth, reproduction and aging which may indirectly affect the global ecology. This is the central focus of this perspective article.

Oxygen Metabolism and Oxidative Stress

The molecular story of oxidative stress commences with consumption of O_2 and oxidation of nutrient molecules to produce energy in aerobes. In the process, mitochondria play a central role. Electron transport chain of mitochondria carries electrons from universal electron donors such as $FADH_2$ and NADH to O_2 via enzyme complexes I, II, III and IV and produces ATP in complex V (Lehninger *et al*., 2008). Incomplete reduction of oxygen molecules and subsequent leaking of electrons in complexes I and III during electron transport, results in formation of superoxide radicals (one of the ROS). Consequently, it leads to formation of other ROS such as hydrogen peroxide and hydroxyl radicals by classical Haeber-Weiss reaction. Cells are equipped with efficient antioxidant defences to neutralize the ROS before they can damage biomolecules by oxidation (Halliwell and Gutteridge, 2008). However, due to decrease in efficiency of antioxidant defenses in response to internal or external insults, generation of ROS are elevated which in turn oxidize all biomolecules present in their vicinity and causes OS in cell. Under such conditions, a deviation in normal physiological functions can not be ruled out which may end up with increase in ratio between energy demand versus production, cell senescence, aging, metabolic depression, retarded growth and reproduction, and finally death may also occurs (Halliwell and Gutteridge, 2008). Therefore, careful and planned study on oxidative stress indices and redox regulatory parameters *in silico* and *in vivo* conditions will have immense importance to solve various riddles observed in several core evolutionary concepts of animal biology such as in life history tradeoffs, senescence, growth, reproduction and sexual selection in free ranging organisms (Costantini *et al*., 2010; Paital *et al*., 2011, 2013, 2015; Paital and Chainy, 2012; Paital and Samanta, 2013, Paital and Chainy, 2014; Paital and Chainy, 2010). Noteworthy, ROS are also reported to be useful because at lower concentrations, they mediate several signal transduction processes in cells (Passos and Zglinicki, 2006; Takano *et al.,* 2003). However, under elevated thermal stress, maintenance of the nominal amount of ROS to regulate signal transduction processes is not ensured (Passos and Zglinicki, 2006).

Aerobes are equipped with both enzymatic as well as non-enzymatic redox regulatory molecules to counteract the over production of ROS to maintain redox homeostasis. Superoxide dismutase (SOD), the first enzyme of enzymatic antioxidant defense, dismutates the toxic superoxide radicals to H_2O_2 and molecular oxygen. H_2O_2 is further neutralized by two cellular enzymes, catalase (CAT) and glutathione peroxidase (GPx). CAT breaks down H_2O_2 to H_2O and O_2 while GPx reduces H_2O_2 and organic hydroperoxides to H_2O and other non-reactive metabolites at the cost of oxidation of a reduced glutathione (GSH) molecule. The oxidized glutathione is reduced back to GSH by the enzyme glutathione reductase (GR) with the help of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) (**Figure 1**). Peroxiredoxins are a group of ubiquitous antioxidant enzymes that regulate the levels of cytokine-induced peroxides (Rhee *et al*., 2005). The oxidized form of peroxiredoxins is non-catalytic in nature. To self recharge after reducing H_2O_2, these enzymes require thioredoxin (Rhee *et al*., 2001). They require electrons from the reduced thioredoxin to restore their enzymatic catalytic function (Pillay *et al*., 2009). Thioredoxins are a class of small ubiquitous redox proteins which also play a key role in removing ROS (Wollman *et al*., 1988; Meng *et al*., 2010). Glutaredoxins are a group of small redox enzymes which confer their antioxidant activity by reducing dehydroascorbate, peroxiredoxins and methionine sulfoxide reductase (Nordberg and Arnér, 2001). Non enzymatic antioxidant defence system comprises of small molecules such as polyphenols, carotenoids, flavonoids, ascorbic acid, vitamin E and GSH which directly scavenge ROS. Under thermal stress, the levels of redox regulatory molecules are found to be alleviated or insufficiently enhanced which fails to combat OS in organisms (Halliwell and Gutteridge, 2008).

The Central Remark

Although not much experimental information is available on positive correlation between rise in temperature and reproduction or growth in fishes in their natural habitat, it is suggested that rise in temperature in combination with elevated CO_2 level decrease the duration of nymphal stadia, the longevity and reproductive success of the aphid *Sipha flava* (Auad *et al*., 2012). Similarly, several authors have pointed out that increase in habitat temperature above 20-24ºC, which is the optimum temperature required for the growth of aphids, can negatively influence fertility, reproduction, development, life expectancy, survival and abundance of aphids (Oliveira *et al*., 2009; Auad *et al*., 2009). A common reason for the above phenomenon is provided that increase in temperature can affect the life cycle of poikilotherms directly by influencing their physiology (Flynn *et al*., 2006). Occurrence of the above multiple processes as the consequences of climatic changes are not only

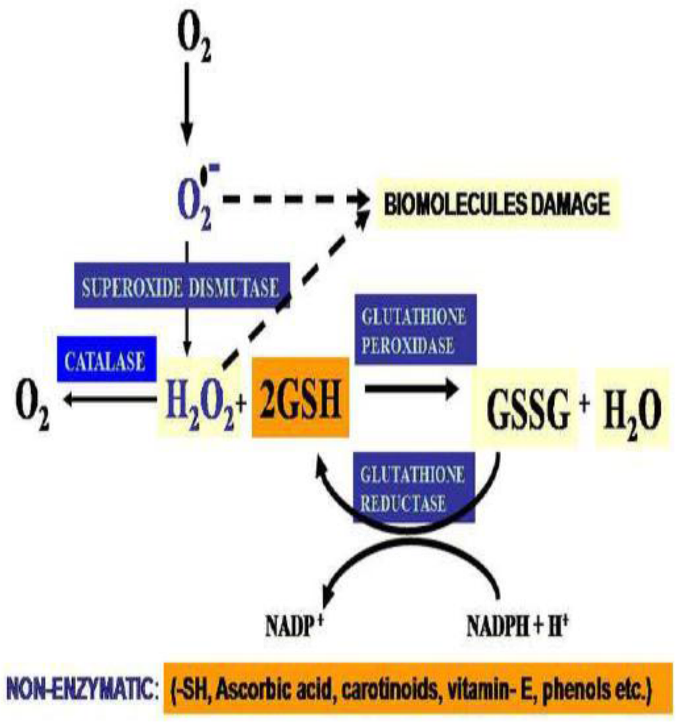

Figure 1: General pathway of oxidative stress metabolism.$O_2^{\bullet -}$- superoxide radicals, GSH-reduced glutathione, GSSG-oxidised glutathione.

restricted to terrestrial ecosystems but also can affect the aquatic ecosystems. For example, in aquatic environment especially in coastal marine bodies, climatic changes also modulate to elevate OS and and its related metabolism as well as negatively modulate the other physiological processes such as reproduction, excretion, respiration of the inhabiting ectotherms (Lawrence and Soame, 2004; Paital and Chainy, 2010, 2012; Abele *et al.*, 2002, 2007, 2011).Increase in salinity can induce OS despite altered redox status found to be initiated to protect poikilotherms (Paital and Chainy, 2010, 2012). With altered redox regulation, fish are also found to experience OS induced by rise in habitat temperature in their natural environment. For example, in cichlid fish acará (*Geophagus brasiliensis*), three-spined stickleback fish (*Gasterosteus aculeatus*), Senegal sole fish (*Solea senegalensis),* environmental rise in temperature induces OS (Table 1). It has been noticed that antioxidant defence parameters changes in fish brain and muscle tissues (*Heteropneustus fossilis)* in response to air exposure due to alteration in functional capacity of electron transport chain (Paital, 2013, 2014). Temperature is known to affect oxygen content of water bodies. Therefore, molecular and cellular functions of fish due to elevated temperature as a consequence of global warming cannot be ignored.

Conclusion

The world is projected to experience an elevation in mean global temperatures in coming years. It is presumed that an

Table 1 Oxidative stress and redox status in natural population of some fish under high habitat temperature.

Name of the Animal	Modulator	Tissue/organ/cell fractions	OS	AOE	Reference
Geophagus brasiliensis (cichlid fish acará)	Comparatively high temperature in spring	Liver	TBARS↑, GSSG↑	SOD↓, CAT	Filho *et al*., 2001
Gasterosteus aculeatus L. (three-spined stickleback Fish)	High temperature in summer with reproductive activity	Liver	TBARS↑	GPx↓	Sanchez *et al*., 2008
Lepomis macrochirus (bluegill fish)	High temperature in summer	Whole animal	NA	NA	Wohlschlag and Juliano, 2003
Solea senegalensis (Senegal sole fish)	High temperature with heavy metal load	Liver	TBARS↑	CAT↓, GPx↓	Oliva *et al*., 2012
Barbus barbus L. (barbell fish)	High temperature in summer	Liver	NA	SOD↓, CAT↑	Radovanovic *et al*., 2010
Barbus barbus L. (barbell fish)	High temperature in summer	Muscle	NA	SOD↓, CAT↑	Radovanovic *et al*., 2010

ROS-reactive oxygen species, OS-oxidative stress (TBARS-thiobarbituric acid reactive substances, PC-protein carbonylation), AOE-antioxidant enzymes (SOD-superoxide dismutase, CAT-catalase, GPx-glutathione peroxidase), GSSG- oxidised glutathione, NA- not analysed. ↓ or ↑ symbols are used to indicate decrease or increase of the parameters with the corresponding season, respectively. Parameter with no symbol (↓ or ↑) indicates “no change” in the same with respect to the season.

approximate rise in temperature of 1.4 to 5.8 0C may occur in next decades (Houghton, 2001). The rise in environmental temperature (thermal stress) of water bodies due to global warming may lead to influence redox homeostasis of aquatic organisms which in turn may be resulted into decrease in normal physiology especially growth and reproduction of poikilotherms in general and fishes in particular by augmenting OS. Therefore, understanding the physiological impacts of global warming in relation to growth and reproduction of fish in their natural environment and development of strategies to manage them are of paramount importance and should be considered as one of the major challenging areas of future research in aquaculture.

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