e-ISSN:2322-0066

Research & Reviews: Research Journal of Biology

# Oxidative stress and ageing in animals under thermal stress due to global warming: A perspective

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## Editorial

Received date: 15/12/2015

Accepted date: 28/12/2015

Published date: 01/01/2016

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**Keywords:** Global warming, rising habitat temperature, thermal stress, mitochondrial dysfunction, reactive oxygen species, oxidative stress, longevity, disease susceptibility, Ageing.

**ABSTRACT**

The world is projected to experience an approximate doubling of atmospheric $CO_2$ concentration coming decades. Increase in $CO_2$ level as one of the most important reasons may contribute to raise the mean global temperature by 1.4-5.8°C. Exposure of animals to thermal stress many times is accompanied with acceleration of certain unwanted biochemical pathways in animals. One of such examples is elevated reactive oxygen species (ROS) and subsequent increase in oxidation of lipids, proteins and nucleic acids by ROS. Increase in oxidation of biomolecules leads to a state called as oxidative stress (OS). OS hampers physiology of animals. Exposure of animals to rise in habitat temperature may also boost animal's metabolism and a positive correlation exists between metabolism and levels of ROS and OS. Continuous induction of OS is negatively correlated with survivability, longevity and positively correlated with ageing in animals. Thus, it can be predicted that continuous exposure of animals to acute or gradual rise in habitat temperature due to global warming is supposed to induce OS and the reduced survibility and longevity in animals. Attribution of global warming to longevity of animals through increase in risk of disease susceptibility via OS also cannot be ignored.

## INTRODUCTION

Climatic change and predicting its consequences on living system are one of the major concerns for the contemporary eco-physiologist. Mainly rise in environmental temperature due to multiple ecological changes is presumed to be a single factor to alter the physiology of the inhabiting organisms. Poikilotherms can be considered as the major targets under rise in temperature of their natural habitat. These organisms do not have physiological mechanism(s) to regulate their body heat in relation to changing environmental temperature. As a result, their energy metabolism is considerably affected by changing environmental temperature [1]. On the other hand, physiological disorders noticed in organisms due to thermal sensitivity in relation to global warming or acute rise in environmental temperature is not only restricted to poikilotherms but also can affect the physiology of homeotherms and plants as well [2]. For example, heat waves generated as a consequence of global warming found to have devastating impacts on plants leading to severe dehydration and drying their foliage parts [3,4]. However, this perspective article is only focused on the influence of temperature due to climate changes especially on animal's oxidative metabolism which influences their other physiology and finally that may govern their survibility and longevity.

Reactive oxygen species (ROS) and other metabolites of oxidative stress (OS) are usually used as biomarkers to study aging in animals. Surplus levels of ROS and oxidative damages impose cells for senescence or aging via important cellular processes such as genomic instability, epigenetic alternation, telomere attrition, mitochondrial dysfunction, deregulated nutrient sensing, intracellular miscommunication and stem cell exhaustion [5]. Exposure of animals to rise in habitat temperature mostly lead to elevated cellular ROS and oxidative damages with alleviated redox capacity. Irrespective of the reasons, elevated temperature may also make the animals susceptible to various diseases that are aggravated under thermal stress. Together, OS and disease

susceptibility may force the animals to age faster under rise in temperature condition. Finally, it may decrease the longevity of animals. In the current article, we propose a perspective by drawing relationships among global warming as one of the reasons of rise in temperature, OS, disease susceptibility, aging and longevity in both poikilotherms and homeotherms.

## THE OXIDATIVE METABOLISM

### $O_2$ consumption, reactive oxygen species and oxidative stress

Oxidative metabolism includes the pathways where $O_2$ performs the central role directly or indirectly to regulate the biochemical processes related to oxidation of nutrient molecules to produce energy in the form of ATP molecules. In the process, the generated reactive oxygen species (ROS: such as superoxide radicals ($O_2^{\bullet -}$), hydroxyl radicals ($^{\bullet}OH$), hydrogen peroxide ($H_2O_2$), hypochlorous acid (HOCl), organic hydroperoxides etc) in cells if not neutralized immediately, can damage the macromolecules non-specifically present in their vicinity which leads to a stress condition more often called as oxidative stress (OS). OS physiology comprises oxygen ($O_2$) respiration by mitochondria, leaking of electrons at complex I and III enzymes of electron transport chains to produce ROS and oxidation of tissues by ROS, responses of both enzymatic (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), peroxiredoxins, thioredoxins etc.) and non-enzymatic (ascorbic acid, glutathione, vit-A etc) redox regulatory molecules against the produced ROS level and generation of ATP molecules etc. OS physiology has immense importance in several core evolutionary concepts of animal biology such as in life history tradeoffs, senescence and sexual selection by analyzing antioxidant defence parameters in free ranging organisms [5,6]. The state of OS in eukaryotes occurs when ROS are over produced or redox state is diminished due to reduced level of redox regulatory molecules in their cells. ROS, such as $O_2^{\bullet -}$, $^{\bullet}OH$ and $H_2O_2$ are generated mainly due to incomplete reduction of $O_2$ during cellular respiration. They are highly reactive in nature can oxidize lipids to lipid peroxide, proteins to protein carbonyls and nucleic acids to their respective adducts [7]. As a result of oxidation of the above biomolecules, reduced efficiency of enzymatic and other functions of proteins, loss of membrane fluidity, unwanted or alleviation in gene expression, complete or partial arrest in several anabolic processes etc. occur in cells. Noteworthy, ROS are also reported to be useful because at lower concentrations, they mediate several signal transduction processes in cells [8,9]. However, under abnormal conditions due to external (mainly environmental including under elevated thermal stress) or internal (cellular) factors, maintenance of the nominal amount of ROS to regulate signal transduction processes is not ensured [8].

Aerobes are equipped with both enzymatic as well as non-enzymatic antioxidant defenses to counteract the over produced ROS. Superoxide dismutase, the first enzyme of enzymatic antioxidant defense, dismutates the toxic $O_2^{\bullet -}$ to $H_2O_2$ and molecular oxygen. $H_2O_2$ (another toxic oxidant) is further neutralized by two cellular enzymes, namely 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 on the cost of oxidation of the reduced glutathione (GSH). The oxidized glutathione is reduced back to GSH by the enzyme (GR) with the help of reduced nicotinamide adenine dinucleotide phosphate. Peroxiredoxins and thioredoxins also contribute to reduce the risk of OS by removing ROS level. Non enzymatic antioxidant defence system comprises of small molecules such as ascorbic acid, vitamin E, GSH etc. which may also scavenge ROS [5,7]. Under thermal stress, the levels of redox regulatory molecules are found to be alleviated or insufficiently increased which fails to combat OS in organisms.

### Mitochondria and the oxidative metabolism

Mitochondria in cells act as the center for ATP anabolism. They act as the main hub for generation of ROS. ROS produced in mitochondria as a result of incompletely reduction of $O_2$ due to leakage of electrons at the complex enzyme centers of inner mitochondrial membrane. In the matrix of mitochondria, a successful electron transport from several universal electron acceptors to $O_2$ molecule leads to produce chemiosmotic gradient across the inter membrane space and matrix [10,11]. As a result, the process is accompanied by $H^+$ pumping into the inter membrane space via complex I, III and IV enzymes and then get back to the matrix via complex V enzyme (ATPase) along its concentration gradient. The free energy available in the last step is coupled with ATP synthesis by the $F_oF_1$-ATP synthase complex and the process is referred as oxidative phosphorylation [12]. Under several pathophysiological conditions, more electrons get leaked particularly at complex I and III enzymes which then reduce $O_2$ to $O_2^{\bullet -}$ [13,14]. $O_2^{\bullet -}$ then becomes the precursor for production of other two ROS $O_2^{\bullet -}$ and $H_2O_2$. It indicates that the process of oxidative phosphorylation includes both the energetic machinery to culminate with ATP production and generation of ROS in the mitochondria. The whole machinery of electron transport chain (ETS) and oxidative phosphorylation work as a function of $O_2$ uptake by the mitochondria. Therefore, measurement of the rate of mitochondrial respiration with oxidative phosphorylation and function of ETC are the important indices for studying the mechanism of ROS generation, OS induction and the energetic status of the organism [5,15].

### Oxidative metabolism induces ageing under thermal stress

### Ageing is one of the major consequences of oxidative stress

One of the important hypotheses of aging postulates that the senescence-associated loss of functional capacity is due to the accumulation of ROS and its consequences as molecular oxidative damage [16]. Aging is characterized by a progressive decline in the efficiency of physiological function and by the increase in susceptibility to disease and finally to death. Continues publications from different research groups indicate that ageing has a strong positive correlation with OS in animals [17,18]. The “free radical

theory of aging" postulates that aging and its related diseases are the consequence of free radical-induced damage to cellular macromolecules and the inability to counterbalance the produced high level of ROS by endogenous anti-oxidant defenses. This leads to alter the nature of membrane fluidity due to lipid oxidation, the reduced enzymatic and other functions of proteins and alternation of gene expression. The origin of this explanation has a foundation in the "rate of living theory" and longevity of an organism is thus supposed to be influenced by its rate of cellular oxidative metabolism especially OS status. In this context mitochondrial rate of ROS production is more important. Indeed, the mitochondrial rate of free radical production seems to have a much stronger correlation with maximum longevity [19].

Temperature has a very strong and positive correlation with cellular levels of both ROS and OS [7]. This particular phenomenon is also found to be true at mitochondrial level in certain ectotherms [20-22]. The main reasons have been attributed to malfunction of the mitochondrial complex enzymes especially complex I and III or over expression of certain complex enzymes with uncoupling between electron transfer or leakage in electron transport chain and oxidative phosphorylation [5,22]. The later case may arrive due to disturbance in chemi-osmotic balance between inter membrane space and matrix of mitochondria. It leads to have less efficient oxidative phosphorylation state/system which leads to less ATP generation. In aquatic ecosystems where temperature is elevated sharply, the availability of environmental $O_2$ also depleted due to its inverse correlation with temperature. Less environmental $O_2$ availability decreases $O_2$ uptake and the final availability of $O_2$ to mitochondria also becomes less. Less $O_2$ in mitochondria may also leads to less ATP generation as $O_2$ is one of the key molecules in the final step reaction of oxidative phosphorylation where it reduced to form water molecule. Less ATP level leads to metabolic depression and in extreme cases it ends in collapsing cellular metabolism and finally death of animals [7]. Mammalian mitochondria also exhibit positive response to temperature to produce ROS. Rise in temperature, therefore, may lead to an undesired state with unfavorable conditions such as cells may experience OS due to high level of ROS, less ATP level and metabolic depression. Insufficient expression or synthesis of redox regulatory molecules under energy deficient condition may also attribute to the high ROS level and OS in animals under thermal stress. High ROS level under thermal stress condition may lead to chromosomal aberrations. High risk of disease susceptibility in animals under thermal stress due to various reasons is also reported [5]. The roles of oxidative stress or ROS as a cause are effects in the above process have been established. Elevated metabolism is reported to increase ROS and OS in animals under rise in temperature stress state [7,21-22]. Therefore the main issue is, altogether, the above reasons may lead to hinder the normal physiology of animals and it may negatively influence the survivability of animals. In extreme cases, animals may encounter permanent metabolic depression. Therefore, continues exposure to gradual or sudden rise in habitat temperature may elevate the oxidative metabolism and can thus adversely influence survibility and finally the longevity of the inhabiting animals. Although, not much experimental information are available directly on correlation between rise in temperature and longevity of animals, Auad et al. [23] suggested that rise is temperature in combination with elevated $CO_2$ level decreases the duration of nymphal stadia, the longevity and reproductive success in *Sipha flava.* The enhancement in global warming is primarily due to increase in atmospheric $CO_2$ level as a consequence of mainly due to anthropogenic activities [24,25]. Therefore, Auad et al. [23] predicted that *S. flava* population may significantly decrease under future climatic conditions when both the concentration of atmospheric $CO_2$ and temperature are projected to increase. Irrespective of the source, rise in $CO_2$ level along with environmental temperature may influence the longevity of animals irrespective of their poikiolo or homeothermic nature. However, the former group of animals is predicted to be more venerable to the above state under rise in global temperature due to lack of ability to regulate their body temperature.

**Ageing in human under thermal stress**

Changes in important abiotic components of complex ecosystem such as climate and weather can disturb the dynamic balance between its biotic and abiotic components [26]. Instability in any ecosystem due to changes in its abiotic components such as temperature can increase the risk of changes in pathogen prevalence, altered pathogen transmission profiles, and increased host susceptibility [27]. These instabilities can have dramatic effects on the health of humans, livestock, wildlife, and marine systems [28-30]. The World Health Organization warned in its 2007 report that infectious diseases are emerging at a rate that has not been seen before. Since the 1970s, about 40 infectious diseases have been discovered, including SARS, MERS, Ebola, avian flu, and swine flu. It was predicted that the ranges of infectious diseases and vectors will be changing in altitude, along with shifts in plant and animal communities and the retreat of alpine glaciers. Additionally, extreme weather events especially gradual increase in global temperature creates conditions conducive to "clusters" of insect-, rodent- and water-borne diseases. Accelerating climate change carries profound threats for public health and society [31]. The key point of presenting such information is that susceptibility of an animal to disease is always has negative correlation with its longevity and a positive correlation with OS. Therefore, attribution of climate change including global warming to longevity of animals including human through different susceptible disease may not be ignored.

**Concluding Remark**

According to Houghton et al. [32], the world is projected to experience an approximate doubling of atmospheric $CO_2$ concentrations to around 700 ppm accompanied by a 1.4-5.8°C rise in mean global temperatures in next decades, and especially $CO_2$ concentrations may reach 770 ppm (IPCC 2007). These climatic changes would greatly alter the survibility and longevity of animals in general and poikilotherms in particular. Oxidative metabolism influenced by rise in environmental temperature due

to climatic changes may be one of the reasons which will influence the normal physiology and longevity of animals **(Figure 1).** Attribution of climate change including global warming to longevity of animals through an increased risk of disease susceptibility cannot be ignored. Therefore, understanding the physiological impacts of global warming in relation to longevity of animals including human being would be one of the central challenges to the biologists of the present millennium.

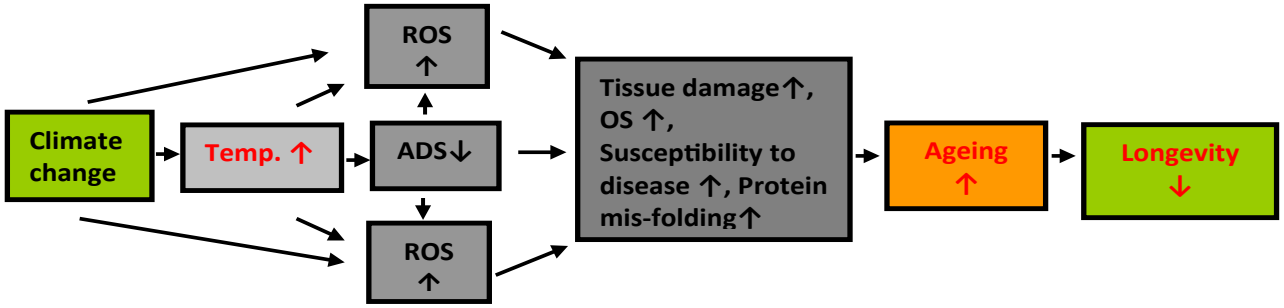


**Figure 1.** Possible correlation between Global warming and longevity modulated by oxidative metabolism. ROS: reactive oxygen species, ADS: antioxidant defense system, S: oxidative stress.

## ACKNOWLEDGEMENTS

Availing Dr.D.S. Kothari PDF fellowship scheme (No. F. 4-2/2006 (BSR)/13-853/2013 (BSR)) funded by University Grants Commission during preparation of this article is duly acknowledged.

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