Longevity of animals under reactive oxygen species stress and disease susceptibility due to global warming

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Abstract

The world is projected to experience an approximate doubling of atmospheric CO$_2$ concentration in the next decades. Rise in atmospheric CO$_2$ level as one of the most important reasons is expected to contribute to raise the mean global temperature 1.4 °C-5.8 °C by that time. A survey from 128 countries speculates that global warming is primarily due to increase in atmospheric CO$_2$ level that is produced mainly by anthropogenic activities. Exposure of animals to high environmental temperatures is mostly accompanied by unwanted acceleration of certain biochemical pathways in their cells. One of such examples is augmentation in generation of 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). Finally, the increase in OS...
condition induces abnormality in physiology of animals under elevated temperature. Exposure of animals to rise in habitat temperature is found to boost the metabolism of animals and a very strong and positive correlation exists between metabolism and levels of ROS and OS. Continuous induction of OS is negatively correlated with survivability and 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 may induce OS, reduced survivability and longevity in animals in general and poikilotherms in particular. A positive correlation between metabolism and temperature in general and altered O\textsubscript{2} consumption at elevated temperature in particular could also increase the risk of experiencing OS in homeotherms. Effects of global warming on longevity of animals through increased risk of protein misfolding and disease susceptibility due to OS as the cause or effects or both also cannot be ignored. Therefore, understanding the physiological impacts of global warming in relation to longevity of animals will become very crucial challenge to biologists of the present millennium.

Key words: Reactive oxygen species; Redox regulation; Oxidative stress; Survivability; Climate change; Disease susceptibility; Global warming; Longevity; Thermal stress

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Core tip: Oxidative damages, generated by reactive oxygen species induce aging in cells via several senescence markers. Thermal stress under global warming can elevate oxidative damages with alleviated redox capacity in animals. Protein misfolding may also occur in animals under such conditions. Elevated temperature may also make the animals susceptible to diseases that are aggrivated under thermal stress. Oxidative stress (OS) and disease susceptibility may push the animals to age faster under thermal stress. We propose a perspective by drawing relationships among rise in habitat temperature, OS, protein misfolding, disease susceptibility, aging and longevity in both poikilotherms and homeotherms.

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INTRODUCTION

Prediction of the impacts of climate change on metabolism of organisms is one of the major concerns for the contemporary eco-physiologist. Rise in environmental temperature due to multiple ecological changes is presumed to be one of the main factors altering the physiology of the inhabiting organisms. Poikilotherms can be considered as one of the major targets to be in trouble under the condition of 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\textsuperscript{[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 are not only restricted to poikilotherms but also can affect the physiology of homeotherms and plants as well\textsuperscript{[2]}. For example, heat waves generated as a consequence of global warming may have devastating impacts on plants leading to severe dehydration and drying their foliage parts\textsuperscript{[3-4]}. However, this article only focuses on the influences of altered temperature due to climate changes especially on cellular active oxygen species metabolism in animals. Because, altered temperature influences physiology and that may govern their survivability and longevity. Emphasis has been paid to draw a positive correlation between oxidative stress (OS) and metabolism of animals. For example, folate metabolism has long been recognized as an important nucleic acid synthesis mechanism for proliferating cells but now it has been discovered that folate metabolism also generates reducing power through producing NADPH. Impaired folate metabolism increases cell sensitivity to OS\textsuperscript{[5]}. Damaging toxicological role of surplus level of reactive oxygen species (ROS) on lipids, proteins, carbohydrates and nucleic acids as a function of thermal stress via multiple cellular processes are discussed in this article. Mitochondria act as the main hub for ROS and OS metabolism\textsuperscript{[6]}. So, emphasis has been paid on the role and distribution of mitochondria in cells of animals on aging as a function of geographical distribution. Finally, correlations have been drawn among OS, metabolism, protein misfolding, disease susceptibility, ageing and longevity in animals. In spite of homeotherms having different adaptive capacity against thermal stress in comparison to poikilotherms, it has been argued, why both are susceptible to toxic effects of ROS and will experience OS under rise in habitat temperature.

ACTIVE OXYGEN SPECIES METABOLISM

ROS are toxic to cells and therefore, studied under toxicology because they non-specifically damage all the cellular biomolecules. ROS or active oxygen species are usually used as ecotoxic biomarkers in various climatic studies\textsuperscript{[5]}. Metabolism of active oxygen species includes the pathways where O\textsubscript{2} performs a central role directly or indirectly to regulate the biochemical processes related to oxidation of nutrient molecules to produce energy. As a result of the above process, different ROS are produced as by-product due to incomplete reduction.
of O₂. Surplus ROS are highly toxic to cells[6]. If the generated ROS in cells are not neutralized immediately, they can damage the macromolecules present in their vicinity in the cells. This ROS induced cellular damage is now well established and is called as OS. Generation of OS in cells is considered as one of the markers of toxicity and is correlated with several senescence related processes. Physiology of OS comprises of oxygen (O₂) respiration by mitochondria, leakage of O₂ to produce ROS and oxidation of tissues by ROS, responses of both enzymatic and non-enzymatic redox regulatory molecules against the produced ROS and oxidative phosphorylation and generation of ATP molecules in mitochondria etc. The state of OS in eukaryotes occurs either due to over production of cellular ROS or due to the diminished redox regulatory capacity to scavenge the (over) produced ROS. Both the above conditions also can arise in cells to generate OS. As stated above, the generated ROS if not neutralized immediately, can oxidize lipids, protein and DNA present in the cells which leads to OS. ROS, such as superoxide radical (O₂⁻), hydroxyl radical and hydrogen peroxide (H₂O₂) are generated mainly due to incomplete reduction of O₂ during cellular respiration. They are non-specifically highly reactive in nature and can oxidize lipids, proteins and nucleic acids to lipid peroxides, protein carbonyls and respective nucleic adducts, few of the important oxidised products of macromolecules, respectively[6]. As a result of oxidation of the above biomolecules, reduced efficiency of enzymatic and other functions of proteins, loss of membrane fluidity, unwanted reduced or alleviation in gene expression, complete or partial arrest in several anabolic processes occur in cells. It is noteworthy that ROS (for example H₂O₂) that are also reported to be useful as at lower concentrations, they mediate several cellular signal transduction processes[7,8]. However, under abnormal conditions due to external (mainly environmental) or internal (cellular) factors including thermal stress, maintenance of the nominal amount of ROS to regulate signal transduction processes is not ensured[7].

Aerobes are equipped with both enzymatic as well as non-enzymatic antioxidant defenses to counteract the over production of ROS. Superoxide dismutase (SOD), the first enzyme of enzymatic antioxidant defense, dismutates the toxic superoxide radicals to H₂O₂ and molecular oxygen[9]. H₂O₂ (another toxic oxidant) is further neutralized by two cellular enzymes, catalase (CAT) and glutathione peroxidase (GPx)[9]. CAT breaks down H₂O₂ to H₂O[11] and O₂ while GPx reduces H₂O₂ and organic hydroperoxides to H₂O 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 with the help of the reduced nicotinamide adenine dinucleotide phosphate. Peroxiredoxins are a group of ubiquitous antioxidant enzymes that regulate the levels of cytokine-induced peroxides[12]. The oxidized form of peroxiredoxins is non-catalytic in nature. To self recharge after reducing H₂O₂, these enzymes require thioredoxin[13]. They require electrons from the reduced thioredoxin to restore their enzymatic catalytic function[14]. Thioredoxins are a class of small ubiquitous redox proteins which also play a key role in removing ROS[15,16]. Their redox functions are mainly due to the reduction of other proteins by cysteine thiol-disulfide exchange[17,18]. Due to the above redox regulatory function of thioredoxins, their roles in reducing OS and decrease in aging have been established in thioredoxin over expressed mice models[19,20]. Glutaredoxins are a group of small redox enzymes which confer their antioxidant activity by reducing dehydroascorbate, peroxiredoxins and methionine sulfoxide reductase[17,21-23]. Non enzymatic antioxidant defence system comprises of small molecules such as ascorbic acid, vitamin E and GSH which directly scavenge ROS[6]. Under thermal stress, the levels of redox regulatory molecules are found to be alleviated or insufficiently enhanced which fails to combat OS in organisms[24] (Figure 1).

**OS, temperature and aging**

A hypothesis describing one of the important causes of aging postulates that the senescence-associated loss of functional capacity is due to the accumulation of toxic ROS and its consequences as molecular oxidative damage[25]. Tissue repair and regeneration is an important topic in aging. The link between aging and inflammation is highlighted in many studies[26]. Chronic, progressive low-grade inflammation can accelerate aging via ROS-mediated exacerbation of telomere dysfunction and, cell senescence, thereby indicating that aging, inflammation, necrosis factor Kb, DNA damage and cellular senescence are closely linked[26]. 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. Publications from different research groups indicate that ageing has a strong positive correlation with OS in animals[27,28]. The “free radical theory of aging” is one of the most plausible and acceptable explanations for the mechanistic basis of aging which 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[29]. This leads to alteration of the nature of membrane fluidity due to lipid oxidation, the reduced enzymatic and other functions of proteins due to oxidation of proteins and alteration of gene expression due to DNA damage. 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 active oxygen species 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...
Climatic factors have significant effects on the active oxygen species metabolism and also on the life cycle of animals \[10,34,35\]. Especially, temperature has a very strong and positive correlation with cellular levels of both ROS and OS \[6\]. This particular phenomenon is also found to be true at mitochondrial level in certain ectotherms \[36-39\].

The main reasons for high cellular ROS and OS are 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 \[40\]. The later case may appear due to disturbance in chemiosmotic balance between inter membrane space and matrix of mitochondria. It leads to a less efficient oxidative phosphorylation state/system which results in reduced rate of ATP generation. In aquatic ecosystems where temperature is elevated sharply, the availability of environmental O\(_2\) is also depleted due to its inverse correlation with temperature. Less environmental O\(_2\) results in decrease in O\(_2\) uptake and the final availability with maximum longevity in animals \[30,31\].

In the modern aging theory, the “rate of living” is defined by metabolism rather than the loss of vital substance, although, advances in aging research continue to challenge this theory. The fiction in modern “rate of living” theory is whether metabolic rate or metabolic stability is the determinant of longevity is still under debate. In a review article, López-Otín et al \[32\] summarized the cellular and molecular hallmarks of aging, and proposed nine candidate hallmarks such as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication. Many of the above factors are directly or indirectly found to be the “cause” or “effects” of OS and ageing in animals \[6\]. Recently, Missios et al \[33\] reported the first experimental evidence that telomere dysfunction enhances the requirement of glucose substitution for the maintenance of energy homeostasis and IGF-1/mTOR-dependent mitochondrial biogenesis in aging tissues.

Climatic factors have significant effects on the active oxygen species metabolism and also on the life cycle of animals \[31,34,35\]. Especially, temperature has a very strong and positive correlation with cellular levels of both ROS and OS \[35\]. This particular phenomenon is also found to be true at mitochondrial level in certain ectotherms \[36-39\]. The main reasons for high cellular ROS and OS are 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 \[40\]. The later case may appear due to disturbance in chemiosmotic balance between inter membrane space and matrix of mitochondria. It leads to a less efficient oxidative phosphorylation state/system which results in reduced rate of ATP generation. In aquatic ecosystems where temperature is elevated sharply, the availability of environmental O\(_2\) is also depleted due to its inverse correlation with temperature. Less environmental O\(_2\) results in decrease in O\(_2\) uptake and the final availability with maximum longevity in animals \[30,31\].
of O₂ to mitochondria also becomes less. Availability of less O₂ in mitochondria may also lead to less ATP generation as O₂ is one of the key molecules in the final step reaction of oxidative phosphorylation where, it is reduced to form water molecule⁴¹. Less cellular ATP level leads to metabolic depression and in extreme cases it ends in with collapse of cellular metabolism and finally death of animals⁹⁰. A positive correlation is also observed between temperature and production of ROS in mammalian mitochondria. Rise in temperature, therefore, may lead to an undesired state with unfavorable conditions such as cellular OS due to high level of ROS, less ATP level and metabolic depression. Insufficient expression of redox regulatory molecules under energy deficient condition may also attribute to the increase in ROS level and OS in animals⁹². The levels of the above state can be augmented under thermal stress. High ROS level under thermal stress condition also may lead to chromosomal aberrations. In totality, the above reasons altogether may direct to hinder the normal physiology of animals and it may negatively influence their survivability under the state of thermal stress. In extreme cases, animals may encounter permanent metabolic depression. Therefore, it can be predicted that continuous exposure to gradual or sudden rise in habitat temperature may elevate the toxic active oxygen species anabolism and can thus adversely influence survivability and finally the longevity of the inhabiting animals.

Although, not many experimental records are available directly on correlation between rising temperature and longevity in animals, Auad et al⁴² observed that rise in temperature in combination with elevated CO₂ level decrease the duration of nymphal stadia, the longevity and reproductive success of the aphid Sipha flava (S. flava). Based on their results, they predicted that populations of the aphid S. flava may significantly decrease under future climatic conditions when the concentration of atmospheric CO₂ and temperature are projected to increase. Similarly, several authors also have pointed that increase in habitat temperature above 20 °C-24 °C (which is the optimum temperature required for the growth of aphids) can directly decrease or negatively influence the fertility, reproduction, development, life expectancy, survival and abundance of aphids⁴³,⁴⁴. Although, effects of temperature on the life cycle and above mentioned related processes were studied in aphids with an objective to control their population for the purpose of pest management, negative influence of rise in temperature on the life cycle of insects in general and aphids in particular cannot be ignored. This is because, both increase in CO₂ level and rise in temperature may affect the life cycle of herbivorous insects indirectly by influencing host plant physiology and phytochemistry⁴⁵. As a result, it affects the food quality and food intake rate of the herbivorous insects⁶⁹. From the above discussion, it seems that focus has been given by researchers to investigate particularly how insects respond to climatic changes⁴⁶-⁴⁸. Global climatic changes may alter ecosystem functioning and species interactions by promoting a shift in the geographical range of herbivores⁴⁹, by facilitating the spread new adventives and invasive species⁵⁰, and by altering the natural climatic control of herbivorous species⁵⁰. As a result, due to a shift of the normal life processes of herbivores, it can affect the life of carnivores by influencing the prey-predator relationship⁵¹,⁵². Occurrence of the above multiple processes as the consequences of climatic changes are not only restricted to terrestrial ecosystems but also can affect the aquatic ecosystems. For example, in aquatic environment especially in coastal marine bodies, climatic changes also negatively modulate the active oxygen species metabolism as well as the other physiological processes such as reproduction, excretion and respiration of the inhabiting ectotherms⁵³. The effects of climate changes on population dynamics of animals are of critical concern⁵⁴,⁵⁵. The enhancement in global warming is primarily due to increase in atmospheric CO₂ level produced from anthropogenic activities and secondarily due to other reasons such as chlorofluorocarbons, halons, methyl chloroform, methyl bromide and carbonetetrachloride⁵⁶-⁵⁸. Irrespective of the sources, rise in CO₂ level along with environmental temperature may influence the longevity of both poikilotherms and homeotherms. However, the poikilotherms are predicted to be more vulnerable to the above state under rise in mean global temperature due to lack of ability to regulate their body temperature⁴¹,⁹⁰. Irrespective of the capacity of thermo regulation in animals, the nature of food habit also can be an indirect factor that may influence the longevity of animals under the rise in environmental thermal stress. This can be correlated to the alterations in biochemistry and physiology in plant tissues under altered climate-controlled conditions. As a consequence, it can affect food quality for herbivores and may modulate the performance of herbivorous animals in general and insect species in particular⁶⁰,⁶¹. Although, elevated CO₂ levels tend to increase the rate of photosynthesis and plant biomass⁶²,⁶³, it reduces host plant quality for herbivores because of increase in foliar carbon and secondary organic compounds⁶⁰,⁶³ and decrease in availability of nitrogen⁶⁴,⁶⁵. Finally, this could indirectly affect all the herbivores in general and arboreal herbivores in particular due to food quality and their host-plant dependency.

**Mitochondria, the main hub for ROS production**

Mitochondria of cells that act as the hub for ATP production are the main centers for generation of ROS or active oxygen species. ROS are produced in mitochondria as a result of incomplete reduction of O₂ due to leakage of electrons at the complex enzyme centers of inner mitochondrial membrane⁶⁶. Especially, leakage of electrons at complexes I and III reduces O₂ for formation of ROS such as O₂⁻, H₂O₂ and “HO (Figure 2). In the matrix of mitochondria, a successful electron transport
from several universal electron acceptors to O\textsubscript{2} molecule leads to the development a chemiosmotic gradient across the inter membrane space and matrix\textsuperscript{[67]}. The process is accompanied by H\textsuperscript{+} pumping into the inter membrane space via complex I, III and IV enzymes and then its back movement into 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\textsubscript{o}F\textsubscript{i}-ATP synthase complex and the process is referred as oxidative phosphorylation\textsuperscript{[68]}. Under several pathophysiological disorder conditions, more electrons leak particularly at complex I and III enzymes which then reduce O\textsubscript{2} to O\textsubscript{2}•\textsuperscript{-}\textsuperscript{[66,70]}. Then the second and third reduction of O\textsubscript{2}•\textsuperscript{-} produces the other two ROS namely the hydroxyl radical (’OH) and H\textsubscript{2}O\textsubscript{2}. It indicates that the process of oxidative phosphorylation includes both, the energy producing machinery culminating with ATP production, and generation of ROS in the mitochondria. The whole machinery of electron transport chain and oxidative phosphorylation works as a function of O\textsubscript{2} uptake by mitochondria. Therefore, measurement of the rate of mitochondrial respiration with oxidative phosphorylation and function of electron transport chain are the important indices for studying the mechanism of ROS generation, OS induction and the energy status of the organism\textsuperscript{[71,72]}. Analysis of OS indices, levels of ROS and redox regulatory parameters has immense importance in several core evolutionary concepts of animal biology such as in life history trade-offs, sexual selection and senescence in free ranging organisms\textsuperscript{[73]}. Therefore, much importance has given to cell senescence and aging in animals in relation to the toxic role of active oxygen species anabolism in mitochondria\textsuperscript{[69]}. Mitochondrial distribution and aging Global warming is likely to uncouple and alter the phase relationships existing between temperature and photoperiod and it may have significant consequences on animal’s reproduction and longevity. For example, it can affect life cycle of organisms that develop gametes during the winter and spawn in the spring in temperate northern latitudes\textsuperscript{[73]}. Therefore, it is predicted that environmental factors related to climate change especially rise in temperature is more likely to have significant impacts on fecundity and spawning success in animals\textsuperscript{[73]}. Ageing and longevity in animals are correlated with each other and the active oxygen species production may act as a link between the above two. Therefore, fecundity and ability of mitochondria in animals in relation to their colder and warmer habitat must have a major role in relation to the current topic. Because mitochondria act as the hub for the production toxic active oxygen species\textsuperscript{[6,36]}. In this context, studies in both laboratory and field intervention indicate that not only temperature acts as a major factor under climate
Although the determining factor is exposure to sunlight faster than that of people who live in colder climates. The skin of people in hot climates certainly seems to age of the skin (which is also a part of ageing and related to longevity. The fact is explained as the increase in aging colder climates (which affects vitamin-D levels) and also shorter life period. The amount of sunlight people get in to hunger and hot climates during generations have northern people live longer and people exposed including human being can be expected. For example, mosses in tundra climate can live up to 150-200 years which is too shorter in warmer regions. noticed that vegetation in colder regions lives longer , issue at “longevity­and­antiaging­secrets.com”.

The longevity of animals living in colder climates should be higher than those live in warmer climates. A very interesting issues, it is pity that there are very few commentaries found in literature. It is speculated that the longevity of animals living in colder climates should be higher than those live in warmer climates. A very relevant logical discussion is made on this particular issue at "longevity­and­antiaging­secrets.com". It is noticed that vegetation in colder regions lives longer, for example, mosses in tundra climate can live up to 150-200 years which is too shorter in warmer regions. The regions are mainly attributed to high fecundity of mitochondria with low cellular metabolic rate. So, it can also be predicted that the more the number of mitochondria, the higher the longevity in animals including human being can be expected. For example, the northern people live longer and people exposed to hunger and hot climates during generations have shorter life period. The amount of sunlight people get in colder climates (which affects vitamin-D levels) and also seasonal disorders can be the reasons to affect human longevity. The fact is explained as the increase in aging of the skin (which is also a part of ageing and related to vitamin-D level) of people who live in sunnier climates. The skin of people in hot climates certainly seems to age faster than that of people who live in colder climates.

Although the determining factor is exposure to sun light rather than temperature, both have always a positive correlation with each other. It can be concluded that with multiple reasons, people living in colder countries have higher life expectancy than the people living in warmer countries. It is observed that in polar countries the life expectancy is > 60 years while it is < 40 years in courtiers present in equatorial lines.

GLOBAL WARMING, HUMAN HEALTH AND AGING

Climate and weather are important abiotic components of complex ecosystems. The dynamic balance between the biotic and abiotic components of ecosystems is often disturbed if changes occur in climate or weather. Instability in any ecosystem due to changes in its abiotic components especially temperature can increase the risk of changes in pathogen prevalence, altered pathogen transmission profiles, and increase in host susceptibility. These instabilities can have dramatic effects on human’s health, livestock, wildlife and marine systems. The World Health Organization (WHO) warned in its 2007 report that infectious diseases are emerging at a rate that has not been seen before. Since the 1970s, more than 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 also. 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 susceptibility to different diseases may not be ignored.

Effects of global warming on human body

A very nice relationship is drawn by Goldsmith et al. among global warming, exposure of human to ultraviolet radiation (UV) (due to depletion of ozone layer) and longevity through disease (such as cancer and increased risk of health disorder processes including immunosuppression) susceptibility. Rise in CO2 level may not be the single factor responsible for global warming. Several chemicals such as chlorofluorocarbons, halons, methyl chloroform, methyl bromide and carbontetra-chloride are also responsible for global warming and they act as ozone-depleting substances too. The ozone layer absorbs most of the UV radiation of sun and protects plants and animals from exposure to such radiation. Fortunately, where a high probability is there for damage of human DNA upon exposure to UV radiation, ozone layer strongly absorbs it. When chlorofluorocarbons
and halons are released into the atmosphere, they rise slowly to reach the stratosphere. Once they reach there, under the influence of the sun's ultraviolet light, chlorine is released and reacts with ozone. As a consequence, depletion of the ozone layer starts. Finally, it ends with hole(s) in ozone layer. When UV and visible radiation from sun strike the skin through such holes in ozone layer, part is remitted, part is absorbed by chromophores in various layers of skin, and part is transmitted inward to successive layers of cells until the energy of the incident beam is dissipated. Two major physical processes namely absorption and scattering with varying wavelengths limit the penetration of UV and visible radiations into skin. UV wavelength less than 320 nm are readily absorbed by proteins, DNA and other components of epidermal cells and UV radiation rays are energetically enough powerful to break the bonds of DNA molecules, and thereby damage cells by the process of mutation, unwanted gene expression, etc. These damaged DNA molecules are not repaired, and can replicate, leading to dangerous forms of skin cancer (basal, squamous, and melanoma). Prolonged human exposure to solar UV radiation may result in acute and chronic health effects on the skin, eye and especially on immune system. Acute complaints like heat strokes, itchy plaques, actinic prurigo, papular lesions, urticaria, photallergy etc. may occur in human. The chronic effects of UV exposure can be much more serious, even life threatening and include premature aging of the skin, suppression of the immune system, damage to the eyes, and finally skin cancer. In the most serious cases, skin cancer and cataracts can occur commonly due to chronic inflammation. According to a report from WHO, a growing body of evidence suggests that environmental levels of UV radiation may suppress cell-mediated immunity and thereby enhance the risk of infectious diseases and limit the efficacy of vaccinations. UV radiation induced immunosuppression and photocarcinogenesis are two important phenomena that can affect human longevity. It is important to note that the immunosuppressive properties of UV radiation refer exclusively to the adaptive immune response. T-cell mediated immune reactions are suppressed on UV exposure but not host defence reaction against bacterial attacks. Under these conditions, the highest risk of skin cancers that appear to accompany is exposure to UV radiation from sun through the holes in ozone layer (that are created indirectly due to global warming). Therefore, direct impact of UV radiation induced immunosuppression on life expectancy is anticipated. The fact is partially supported by a study over 300000 people born in Maine. The people who were born in a peak solar year lived 1.5 years less than those born in non-peak years.

Global warming and vector born diseases

ROS produced by phagocytes are critical for host defense against infection. The negative regulator of ROS production, which is localized to the endoplasmic reticulum of phagocytes, has been discovered. On the other hand, climate change and its effects on emerging infectious diseases were elegantly predicted by Epstein in 2001. Especially infection rate of diseases those are insect vector born can be aggravated in comparatively warming habitats. For example, diseases carried by mosquito vectors are particularly sensitive to meteorological conditions. Excessive heat kills mosquitoes, but within their tolerance and survivable range, warmer temperatures increase both their reproduction and biting activity and the rate at which pathogens mature within them. McArthur had determined in 1972 that at 20 °C, Plasmodium falciparum, a malaria causing protozoa, takes 26 d incubation time but just at rise in 5 °C higher temperature, i.e., at 25 °C, they develop in 13 d. So, warmer temperatures could mean longer and more frequent waves of mosquito infestations. A very small change in the Earth’s temperature has a big impact on the above process. The longevity of Anopheles mosquitoes, the carriers of malaria is only few weeks. Therefore, increase in temperature, permits the parasites to mature in less time in the body of mosquito to transfer the infection. Due to the temperature thresholds in Anopheles mosquito, the transmission of falciparum malaria occurs where temperature exceed 16 °C. The mosquito Aedes aegypti, who acts as vector for both yellow and dengue fever, is restricted by the 10 °C winter isotherm. Temperature less than that can slow their life cycle and under freezing temperatures, eggs, larvae and adults of Aedes are killed. Expanding tropical conditions can also elevate the transmission rate of the disease. Warm nights and warm winters favour insect survival. Therefore, rise in temperature can be positively correlated with the risk of disease susceptibility in human and it can affect the longevity.

Temperature, protein misfolding, diseases and longevity

One of the vital elements required for maintenance of the structural architecture of cells is protein. At least 30000 different proteins with a different role are identified in humans. The main functions of proteins in all organisms are to make cellular building blocks and to operate cellular functions. To fulfill specific function(s), each protein has to maintain its own unique sequence and shape in native conformation. Protein folding is the process by which the newly synthesized protein molecule folds into its unique, three-dimensional native structure. The sequence of protein synthesis in relation to folding may be described as the synthesis of primary amino acid chains (peptides) which joined together to form secondary α-helix and the β-sheet and random coils of peptides. It can further fold to have the tertiary structure refers to the distribution of both α-helices and β-sheets and random coils in the protein, wherein, these elements are folded into a compact conformation stabilized by hydrogen bonds or
ionic interactions\textsuperscript{(101)}. These are referred as monomeric proteins. The monomeric proteins after formed in three-dimensional structure can become multimeric form and the conformation is called as quaternary structure of proteins in which the different polypeptide chains are connected. The required native conformations of proteins in cells are achieved by post translational modifications including folding\textsuperscript{(101)}.

Several molecular and cellular mechanisms are associated with protein folding. One of such examples is the involvement of chaperons\textsuperscript{(102)}. On the other hand, synthesis of incorrectly shaped (misfolded) proteins occurs in cells due to many factors. One of such factor is exposure to environmental changes\textsuperscript{(99)}. More specifically the degree of misfolding can increase due to exposure of animals to increase in temperature, high or low pH, agitation, elevated glucose, or oxidative damages. For examples, misfolding or denaturation of streptokinase\textsuperscript{(103)} and β-lactoglobulin\textsuperscript{(104)} at increased temperature and SO\textsubscript{4}\textsuperscript{2-} (105), LDL, ApoC-II \textsuperscript{(106,107)} due to oxidative damages are reported. The rate of misfolding is accelerated by the altered amino acid composition in proteins due to mostly mutations. Protein misfolding and the subsequent aggregation are associated with various, often highly debilitating, diseases for which no sufficient cure is available yet. Although, many recent efforts have been made to develop treatments for diseases associated with protein misfolding, not much success has been achieved. Diseases that are associated with protein misfolding represent a group of disorders that have protein aggregation and plaque formation in common\textsuperscript{(108)}.

Amyloidosis is a group of such protein misfolding diseases, in which protein aggregates accumulate either systemically or locally in certain organs or tissues. Other neurodegenerative diseases namely Alzheimer’s disease (Amyloid-β, tau), Parkinson’s disease (α-synuclein), Huntington’s disease (Huntington), familial British dementia (Ab), Spongiform encephalopathies (Prion), hereditary cerebral hemorrhage with amyloidosis (cystatin C), amyotrophic lateral sclerosis (CuZn SOD) and other diseases such as diabetes mellitus (IAPP, amylin), atherosclerosis (modified lactate dehydrogenase) and sickle cell anemia (hemoglobin) are found to be the leading protein disorder related diseases\textsuperscript{(99)}. These protein misfolding diseases share similar pathological aspects including hypertension, OS, or hyperglycemia, and all of these can result in protein misfolding\textsuperscript{(101)}. All the above diseases or pathways are found to be influenced by climatic changes in animals. It is now clear that both temperature and OS cause protein misfolding and associated diseases. Particularly, protein misfolding is highly temperature dependent\textsuperscript{(108,109)} and under rise in environmental temperature, the risk of disease susceptibility is also predicted to influence ageing and longevity in animals via protein misfolding. Therefore, rise in environmental temperature can raise OS in one hand and increases the risk of protein misfolding and disease susceptibility on the other hand in animals including humans. As a result it can influence the longevity in animals.

**ADAPTATION OF ANIMALS AND OS UNDER HIGH HABITAT TEMPERATURE**

**Adaptation mechanism and OS in animals**

Many animals including vertebrates maintain various long or short term adaptation strategies to cope with fluctuation in environmental temperature. Hibernation and aestivation are two such examples during which animals cope with fall or rise in environmental temperature, respectively. Aestivation is a state of dormancy or seasoning noticed in animals and is characterized by inactivity and metabolic depression in response to high temperatures and arid conditions\textsuperscript{(110)}. It takes place during times of hot and dry season of the summer months. Fossil records show that the act of aestivating may be several hundred million years old. The depression of metabolic rate during aestivation causes a reduction in macromolecule synthesis and degradation. To stabilize the macromolecules, aestivators usually enhance antioxidant defenses and elevate chaperone proteins. At such time period, metabolic depression related responses such as tissue specific large glycogen reserves, anaerobic glycolysis, attempt for reduced ATP generation and energy utilization with specific biochemical and transductional adjustments are few of the strategies adapted by animals to avoid environmental insults especially hyperthermia states\textsuperscript{(20,111-115)}. Increase in redox status or low O\textsubscript{2} uptake are also two other strategies adapted by animals to keep the cellular ROS level low with reduced OS level\textsuperscript{(39,41,116)}.

This is one of the widely used strategies adapted across all forms of hypometabolism. These physiological and biochemical concerns appear to be the core elements of hypometabolism throughout the animal kingdom\textsuperscript{(117)}. For example, the above phenomenon is observed in insects such as lady beetles (Coccinellidae)\textsuperscript{(118)} and mosquitoes\textsuperscript{(119)}, in Australian land snail Rhagada tescornus\textsuperscript{(120)}, in amphibians such as Broomistega putterilli\textsuperscript{(121)} and California red-legged frog and in water-holding frog\textsuperscript{(122)}, in African lungfish\textsuperscript{(123,124)}, in mammals\textsuperscript{(125)} such as Malagasy fat-tailed dwarf lemur\textsuperscript{(126)} and East African Hedgehogs\textsuperscript{(127)}.

From the above discussion, it is expected that under high temperature in summer season, the aestivating animals due to adaptation especially metabolic depression (here it is an adaptation) and in non-aestivating animals due to long term adaptation to temperature\textsuperscript{(128)}, rise in OS is not expected\textsuperscript{(15)}. And, the phenomena must be true in natural populations. However, reports on natural populations of several groups of animals including ectotherms (sensitive to temperature) indicate that they experience OS under rise in temperature in summer season\textsuperscript{(129-134)} (Table 1). Their redox regulatory capacity via different antioxidant molecules became insufficient to neutralize the over produced toxic ROS and it induces cellular OS under rise in temperature condition (Table

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**Table 1:**

| Species                          | Redox Regulatory Capacity |
|---------------------------------|----------------------------|
|                                 |                            |

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1). Such observations refuse the general idea that long or short term adaptations such as aestivation or altered redox regulatory system do not protect the animals from OS under rise in temperature condition in summer.

Table 1 Oxidative stress and redox status in natural population of various animals under high habitat temperature

| Name of the animal | Modulator | Tissue/orga/organ cell fractions | ROS | OS | AOE | Ref. |
|--------------------|------------|----------------------------------|-----|----|-----|------|
| Mytilus spp. (bivalve) and Macoma balthica (bivalve) | High temperature in summer | Whole animal | NA | NA | NA | [129] |
| Anodonta anatina freshwater duck mussel | High temperature in summer | Whole animal | NA | NA | [130] |
| Perna viridis (green-lipped mussel) -do- | Low temperature Winter | Digestive gland | HO2 | TBARS | SOD, GPx | [131] |
| -do- | -do- | Gills | HO2 | TBARS | SOD, GPx | [131] |
| Crassostrea rhizophorae (mangrove oyster) | High temperature in summer | Digestive gland | NA | TBARS | SOD, CAT | [131] |
| | | Gill | NA | Lipid | CAT | [132] |
| Viviparous arterios (river snail) | High temperature in summer | Whole body | NA | NA | SOD, CAT, GPx | [133] |
| Ancylus fluviatilis (liplet) | High temperature in summer | NA | NA | NA | [134] |
| Nacella (Patinigera) magellanica (limpet) | High temperature in summer | Whole body (for O3 consumption), Digestive gland | NA | SOD, CAT | GPx | [135] |
| Gammarus roeseli (freshwater gammarid crustacean) | High temperature in summer | Tissue pool | NA | MDA | CAT, GPx | [136] |
| Scylla serrata (mud crab) | High temperature in summer with high salinity | Hepatopancreas | HO2 | TBARS, PC | SOD, CAT, GPx | [34] |
| -do- | -do- | Muscle | HO2 | TBARS, PC | SOD, CAT, GPx | [34] |
| -do- | -do- | Gill | HO2 | TBARS, PC | SOD, CAT, GPx | [34] |
| Geophagus brasiliensis (cichlid fish acará) | Comparatively high temperature in spring | Liver | NA | TBARS, GSSG | SOD, CAT | [137] |
| Gasterosteus aculeatus L. (three-spined stickleback fish) | High temperature in summer with reproductive activity | Liver | NA | TBARS | GPx | [138] |
| Lepomis macrochirus (bluegill fish) -High | High temperature in summer | Whole animal | NA | NA | NA | [139] |
| | temperature with high salinity | | | | | |
| Solea senegalensis (Senegale snail) -do- | High temperature with heavy metal load | Liver | NA | TBARS | CAT, GPx | [140] |
| Barbus barbatus L. (barbell fish) -do- | High temperature in summer | Liver | NA | NA | SOD, CAT | [141] |
| -do- | -do- | Muscle | NA | NA | SOD, CAT | [141] |
| Trachemys scripta elegans (red-eared sliders Turtle) | High temperature in summer | Whole animal | NA | NA | NA | [142] |
| Caiman yacare (crocodile) | High temperature in summer | Liver, Kidney, Lung | GSSG | NA | NA | [143] |
| Tupinambis merianae (tegu lizard) | Low temperature in winter | Whole animal | NA | NA | NA | [144] |
| Rana ridibunda (frog) | High temperature in summer | Liver | NA | TBARS, PC | SOD, CAT | [144] |
| Eurocephalus schellenberg (scyphelles warbler bird) | Low food availability | Blood | NA | hydroperoxides | NA | [145] |
| Perdica asiatica (bird) | High temperature in summer | Lungs | NA | MDA | SOD, CAT | [146] |
| Hirundo rustica L. (Barn Swallow) bird | Summer with higher temperature | Liver | NA | Lipid | CAT | [147] |
| | | | | | | |
| Hirundo rustica L. (Barn Swallow) bird | Pre egg laying time | Blood plasma | NA | MDA, PC | NA | [148] |
| Halichoeres grypus (Grey seal) | Summer (No variation in temp) | Whole animal | NA | NA | NA | [149] |
| Ovis aries (Rasa Aragonesa rams) | Breeding season with high temperature | Semen | NA | NA | SOD, CAT, GPx | [150] |
| Bos Taurus (simmental bulls) | High temperature in summer | Semen | NA | TBARS, PC | GPx (highest | [151] |
| | | | | | in autumn) | |
| (Kuroge washu) Japanese Black cow -do- | High temperature in summer | Blood | NA | TBARS | SOD, GPx | [152] |
| Rattus norvegicus (Wistar rats) | Short photoperiod exposure in winter | Erythrocytes | NA | TBARS | NA | [152] |
| Guinea-pigs | High temperature in summer | Heart | O2↑ | NA | SOD | [153] |
| Rattus norvegicus (Wistar rats) | High temperature in summer | Heart | O2↑ | NA | SOD | [154] |
| Homo sapiens | High temperature in summer | -- | NA | 8-isoprostane | NA | [154] |

ROS: Reactive oxygen species; OS: Oxidative stress; MDA: Malondialdehyde; 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.
lives in ambient temperature of about 30°C. These mechanisms act through the autonomic nervous system to maintain near-constant activity temperatures across a wide range of environmental temperatures. However, poikilotherms (for example in lizard) in comparison to homeotherms (for example in mouse) over a wide range of temperature (4-43°C) becomes different. In extremes cases, under high environmental temperature or continuous exposure of animals to increase in state of environmental temperature may result in failure to maintain normal body temperature in animals. The above discussed mechanism may not work properly under gradual and long-term exposure of homeotherms to not only increase but also decrease in either side of their ambient environmental temperature. Under increase in body temperature, death may result due to heat exhaustion or uncontrolled hyperthermia. Under high temperature, homeotherms also adopt some physiological balance to decrease their metabolic rate. It indicates that under elevated temperature, homeotherms may dissipate their body heat up to certain extent in a time dependant manner. The main metabolic response, i.e., sustained energy output in poikilotherms (for example in lizard) in comparison to homeotherms (for example in mouse) over a wide range of temperature (4-43°C) becomes different. In the former one, the energy output may show a steady increase up to 25°C-30°C followed by a sharp fall in season. So, these animals also can be susceptible to OS and ageing under rise in environmental temperature.

**Poikilothermy vs homeothermy under rise in environmental temperature condition**

In relation to the present context of the production of toxic ROS under the elevated environmental temperature condition, the susceptibility of homeotherms than poikilotherms offers a debate. Poikilotherms are the organisms whose body temperature varies considerably with the ambient environmental temperature. Many terrestrial and aquatic ectotherms are categorized under this group. Vertebrates, specifically fish, amphibians, and reptiles, as well as a large number of invertebrates are studied under the group poikilotherms. The naked mole-rat is believed to be the only poikilothermic mammal. On the other hand, homeotherms can thermoregulate for a stable internal body temperature regardless of environmental heating. However, the thermoregulation capacity works in homeotherms to maintain constant body temperatures through behavioral mechanisms alone i.e., behavioral thermoregulation. Many reptiles use this strategy. For example, desert lizards are remarkable in that they maintain near-constant activity temperatures that are often within a degree or two of their lethal critical temperatures. Temperature regulatory mechanisms act through the autonomic nervous system and are largely controlled by the hypothalamus of the brain, which responds to stimuli from nerve receptors in the skin, e.g., more active sweating in response to continued heat and an increase in subcutaneous fat deposits in response to continued cold.

In mammals including humans, temperature regulation represents the balance between heat production from metabolic sources and heat loss from evaporation (perspiration) and the processes of radiation, convection, and conduction. In a cold environment, body heat is conserved first by constriction of blood vessels near the body surface and later by waves of muscle contractions, or shivering, which serve to increase metabolism. Shivering can result in a maximum fivefold increase in metabolism. Therefore, this mechanism may not be sufficient for a naked person to increase the metabolic rate to replace heat lost to the environment at below 40°F (4°C). Another heat-conserving mechanism observed in goose bumps, or piloerection. It raises the body hairs; although not especially effective in humans, in animals, it increases the thickness of the insulating fur or feather layer. However, it is a time dependant and species specific response that can save the animal from the cold environment. On the other hand, in a warm environment, heat must be dissipated to maintain body temperature. In humans, increase in surface blood flow, especially to the limbs, acts to dissipate heat at the surface. At environmental temperatures above 34°C, or at lower temperatures when metabolism has been increased by work, heat must be lost through the evaporation of the water in sweat. People in active work may lose as much as 4 quarts per hour for short periods. However, when the temperature and humidity are both high, evaporation is slowed, and sweating is not effective. Most mammals do not have sweat glands but keep cool by panting (evaporation through the respiratory tract) and by increased salivation and skin and fur licking.

A low rate of acclimatization in homeotherms occurs when they are continuously exposed to heat or cold. In extremes cases, under high environmental temperature or continuous exposure of animals to increase in state of environmental temperature may result in failure to maintain normal body temperature in animals. The above discussed mechanism may not work properly under gradual and long-term exposure of homeotherms to not only increase but also decrease in either side of their ambient environmental temperature. Under increase in body temperature, death may result due to heat exhaustion or uncontrolled hyperthermia. Under high temperature, homeotherms also adopt some physiological balance to decrease their metabolic rate. It indicates that under elevated temperature, homeotherms may dissipate their body heat up to certain extend in a time dependant manner. The main metabolic response, i.e., sustained energy output in poikilotherms (for example in lizard) in comparison to homeotherms (for example in mouse) over a wide range of temperature (4-43°C) becomes different. In the former one, the energy output may show a steady increase up to 25°C-30°C followed by a sharp fall in...
While in the later i.e., in homeotherms, the temperature range on energy output is very narrow being 30°C to 40°C with a peak at about 38°C ([158-160]). The homeotherm has a much higher output, but can only function over a very narrow range of body temperatures and such situation may arrive under a gradual and long term exposure of homeotherms to increase in environmental temperature. So, in homeotherms, elevated temperature with elevation in high energy output can be correlated primarily with the increase in metabolism and secondarily with the increase in ATP production rate coupled with rapid electron transfer in ETC. It may then favor electron leakage at complex enzymes, i.e., at complex I and III and production of ROS ([36]) (Figure 2). On the other hand, although the metabolic rate of homeotherms is proposed to be faster in colder temperatures than in warmer temperatures since they have to create their own warmth to maintain constant body temperature ([6,41]), the change in temperature from cold to warm may also cause a rise in the metabolic rate in homeotherms. Because their oxygen needs will increase as they regulate their body temperature. Several studies also confirm that elevated temperature causes increase in O₂ consumption in mammals ([60,61]) (Figure 4). It is noteworthy to mention that in context dependant manner, either increase or decrease in O₂ consumption may result when habitat temperature is changed especially when elevated (which may arrive due to global warming).

On the other hand, due to the altered O₂ concentration in environment or due to altered metabolic status of homeotherms, they may experience hypoxia or hyperxia under elevated or reduced environmental temperature condition. Both hyperxia and hypoxia are known to induce ROS and OS in animals including homeotherms ([6,41]). Altogether, higher or lower oxygen consumption, increased metabolism, increase in energy demand at elevated temperature may increase the risk of increase in ROS production. This is because, all the above processes are known to be positively correlated with ROS generation ([6,41,162]). Therefore, with a much higher energy output only over a very narrow range of body temperatures (35°C-40°C), homeotherms are also entitled to experience high ROS level in their cells under elevated temperature conditions. Therefore, under continuous and gradual increase in environmental temperature, both the homeotherms and poikilotherm may experience OS and that can affect their longevity.

CONCLUSION

According to Houghton et al. ([163]), the world is projected to experience an approximate doubling of atmospheric CO₂ concentrations to around 700 ppm accompanied by a 1.4°C-5.8°C rise in mean global temperatures in the year 2100. These climatic changes would greatly alter the survivability and longevity of animals in general and poikilotherms in particular. Production of active
oxygen species influenced by rise in environmental temperature due to climatic changes may be one of the major reasons that are expected to influence the normal physiology and longevity of animals (Figure 5). Risks of climatic change especially global warming on longevity of animals through an increase in risk of disease susceptibility, protein misfolding, lowering ATP generation and several other factors (Figure 5) that boost aging in animals can not be ignored. Therefore, understanding the physiological impacts of global warming in relation to longevity of animals including human being would be one of the major challenges to the biologists of the present millennium.

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