Review article

Oxidative Stress and Aging
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Abstract:
Ageing is an inevitable life process characterized by a gradual functional decline of all organ systems occurring at the cellular, tissue, organ and whole body levels further leading to the development of diseases and finally death. Although aging is a normal physiological process, it can be accelerated during oxidative stress or during chronic inflammatory conditions. An appropriate theory must explain four main characteristics of ageing: it is endogenous, progressive, irreversible and deleterious for the individual. Oxidative stress is caused by imbalance between oxidants and antioxidants. Reactive Oxygen Species (ROS) not only cause cell damage, but are also involved in intracellular signaling. ROS include superoxide (\(O_2^-\)), hydrogen peroxide (\(H_2O_2\)), hydroxyl radical (OH\(^-\)) and peroxynitrite. Various enzyme systems produce ROS including the mitochondrial electron transport chain, cytochrome P\(_{450}\), lipoxygenase, cyclooxygenase, the NADPH oxidase complex, xanthine oxidase and peroxisomes. More research is needed to explain the exact mechanisms related to ageing and oxidative stress.

Keywords: ageing; oxidative stress

Introduction
People all over the world are now living longer than before, mainly due to the improvement in the health sector, treatment of infectious diseases and possibly better nutrition\(^1\). Ageing is a complex and adaptive process characterized by diminished homeostatic response resulting from accumulated physiologic, biochemical, psychological and social wear on the organism overtime\(^2\) that leads to morbidity and mortality\(^3\). According to Strechler and Mildvan, ageing is defined as universal, progressive, intrinsic and degenerative process\(^4\).

The term oxidative stress was first used in 1950 by researchers who described the toxic effects of ionizing radiation, free radicals and oxygen\(^5\) and the cumulative adverse effects of such processes responsible for the phenomenon of ageing\(^6\). Oxidative stress has been correlated to ageing and many other conditions such as Alzheimer disease, cardiovascular disease, diabetes, Parkinson’s disease, Huntington’s disease, cataract and cancers\(^7\)-\(^11\). There are many theories of the aging process, but they can be classified into evolutionary and physiologic. Physiological processes that may explain ageing include oxidative stress, immunologic, neuroendocrinologic, metabolic, insulin signalling and caloric restriction. According to the theory of evolution, natural selection declines with age\(^12\). This theory suggests that ageing will result from accumulation of multiple unrepaired faults. The Disposable soma theory\(^13\) also resembles antagonistic pleiotropy, but differs from the latter in terms of resource allocation between reproduction and somatic maintenance. The free radical theory of ageing is the most updated theory and the concept of free radicals playing a role was described by Harman 1956\(^7\). Elevations in the levels of oxidizing species generation from phagocytes without a concomitant rise in the reducing power was shown starting at age 40 in spite of marked fall in the reducing power starting at only year 50\(^14\). Oxidative stress has been associated with atherosclerosis and cardiovascular disease\(^15\), schizophrenia or atlentran deficit hypersensitivity disease\(^16\). Although the oxidative stress hypothesis of ageing continues to be related to pathophysiological alterations, yet it is also a subject of ongoing debate\(^17\). Much controversy regarding the role of reedox homeostasis in ageing is based on the fact that most research on ROS dependent mechanisms has been done on species which are relatively short lived. But researchers in favour of this oxidative stress theory\(^18\) focus on phylogenetically diverse species with extreme longevity and identifying the causative mechanisms making them differentiated from short lived related species\(^19\). Although the ageing process

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seems to be similar among mammalian species, yet the state of ageing differs remarkably from short lived species such as mice (which live up to 4 yrs of age) to humans (who may live more than 100 yrs) or certain whale species, which may live multiple centuries. Previous studies proved to be markedly useful in comparing the oxidative stress hypothesis of ageing in mammal and avian species.

Many ROS species are involved in oxidative damage in cells causing modification of the free radical theory of ageing. Long lived species have shown reduced oxidative damage, reduced mitochondrial ROS production, increased antioxidant defenses, and increased resistance to oxidative stress both in vivo and in vitro. However, some studies have shown that there is no correlation between oxidation with life span or even longer life span has been correlated with increase in oxidative stress. The results of life span studies from invertebrate models have been confusing so that some models show significant alterations in life span, but others may not show complex alteration. However, over expression of these antioxidants might extend the life span of this model organism. On the other hand, superoxide dismutase in roundworm C. elegans may not show any change in lifespan or may show increased life span, although the sensitivity of worms to oxidative stress is increased and the accumulation of oxidized proteins is enhanced.

In Drosophila, over expression of these enzymes and various antioxidants such as catalase, thioredoxin and methionine sulfoxide reductase has either enhanced the life span or had no effect. The life span in females and males is also different. Jose Vina et al. have shown that females live longer than males. Borras C in their study showed that in mice and rats have shown that mitochondria from female rats produce about twice as much as H$_2$O$_2$ as compared to male rats. Moreover, ovarian hormones such as estrogens have correlation with mitochondrial $H_2O_2$ production. However, with the estrogen replacement therapy, the observed increase in $H_2O_2$ production as a result of ovariectomy was totally abolished. Estradiol upregulates GPX and Mn-SOD expression mediated by NFkB. Various workers have shown that the expression of NADPH oxidase is higher among males than females and this leads to increased NADPH oxidase dependent superoxide anion formation in males as compared to females in the aorta and in the cerebral vasculature. Pinto et al. reported that glutathione peroxidase activity was higher in females than males. But these authors did not relate this fact to the different longevity between males and females. Molecular expression of glutathione peroxidase gene is markedly low in males as compared to females.

Regarding survival (repair) responses to oxidative stress and ageing, several DNA repair systems have been developed depending upon various DNA lesions. In humans and mice, mutations in certain DNA repair genes cause phenotypes of ageing. The capacity of base excision repair declines with aging, accompanied by decrease in the activity of 8-oxoguanine-DNA glycosylase (Ogg1). As a result, 8-oxoguanine lesions accumulate with ageing. In mammalian cells, heat shock proteins (HSP) are synthesized on exposure to oxidative stress after the heat shock response is activated and translocated to the nucleus of one or more heat shock transcription factors. These factors control the expression of a set of genes encoding cytoprotective HSP. The HSP expression increases with ageing in rats in response to age associated accumulation of protein damage by oxidation.

Regarding methylglyoxal, high levels can increase ROS production and cause oxidative stress. Methylglyoxal, is a highly reactive electrophilic and β-dicarbonyl aldehyde compound formed mainly during glycolysis. Plasma methylglyoxal are increased in diabetes. Increased methylglyoxal and other reactive aldehydes like glyoxal and 3-deoxyglucosone (3-DG) leads to carbonyl overload and stress in many candidates like hypertension, atherosclerosis, diabetes, and neurodegenerative disease. But studies in hypertensives have shown the increased MG formation could be due to increased production rather than reduced degradation. Activity of the glyoxalase system depends on adequate levels of GSH. However MG makes cells more sensitive to oxidative stress by depleting GSH & oxidative stress also depletes GSH. MG leads to increased production of superoxide and oxidative stress through its actions on mitochondria, provide ATP for body use and also generate about 85% of total intracellular superoxide during the process of energy production. A study by KM Desai et al. has shown that MG causes mitochondrial oxidative stress by increasing the generation of mitochondrial superoxide, nitric acid and peroxynitrite and also the activities of Mn-Sod and complex III are significantly reduced by MG. MG can also cause oxidative stress indirectly through generation of most intracellular and extracellular AGES. Advanced glycation end products (AGES) are also correlated to ageing.
diabetes, inflammation and neurodegeneration. AGES also contribute to many other chronic diseases like nephropathy, vascular disease, amilodosis and cancer via binding to cellular surface receptors (RAGE). ROS are involved in AGE signalling through RAGE.

Genotoxicity of AGES involves oxidative stress and angiotensin 2, type 1 receptors. AGES regulate expression of vascular endothelial growth factors and induce apoptosis in fibroblasts through activation of ROS. The function of retinal microglia in rat may be altered by AGES by up regulating TNF-alpha expression and formation of ROS, which can further activate other signalling pathways. RAGE is involved in the pathogenesis of ischemia reperfusion injury and inflammatory reactions during tumor development. AGES also increase endothelio permeability. Recently developed compound called alagebrium may be useful in reducing MG and ultimately AGES induced oxidative stress, thus slowing the ageing process. Alagebrium in addition to other beneficial effects, also increased SOD and glutathione peroxidase activities in ageing hearts and cultured cardio myocytes.

Caloric restriction is known to reduce oxidative stress and prevent or slow the process of ageing by reducing the metabolism of ROS production. This will further prevent oxidative damage to biomolecules, prolonging the lifespan. Roux et al has shown the beneficial effect of caloric restriction in fission yeast schizosaccharomyces peombe. A study by Hippkiss

90,91 has shown that intermittent feeding can produce metabolic effects similar to those produced by caloric restriction such as reduced formation of MG and help in delaying of ageing process thus prolonging the life span. This is an adaptive response known as hormesis, which increases life span. Sirtuin SIRT 1 expression and activation can be affected by many cellular conditions like caloric restriction, exercise and oxidative stress. Sirtuins are mammalian homologues of Sir2 and are class III histone deacetylases. There is need for more research to determine the exact mechanisms related to ageing and oxidative stress with further aim to postpone senescence or age with utmost health. New antioxidant strategies are needed to clarify the role of antioxidant therapy in cardiovascular diseases.

**Conclusion**

Ageing is a multifactorial process involving changes at the level of cell, tissue, organ and the whole body resulting in decreased functioning, development of diseases and ultimately death. So oxidative stress is the consequence of an excess of metabolic oxidant species at the level of biomolecules and is related to ageing and age related diseases. So oxidative stress is caused by imbalance between oxidants and antioxidants. Among all the theories of ageing, the most updated one describes the role of ROS in the ageing process. Further research is needed to establish the exact mechanisms related to ageing and oxidative stress.
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