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International Journal of Current Research
Vol. 9, Issue, 07, pp.53518-53528, July, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

VARIOUS FACTORS INVOLVING AGING: ELECTRON TRANSFER, REACTIVE OXYGEN SPECIES AND OXIDATIVE STRESS

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ARTICLE INFO

Article History:
Received 29th April, 2017
Received in revised form
11th May, 2017
Accepted 07th June, 2017
Published online 22nd July, 2017

Key words:
Reactive Oxygen Species,
Reactive Nitrogen Species,
Oxidative Stress, Electron Transfer,
Antioxidants, Radicals, Aging,
Stem Cells, Protein Oxidation,
Mitochondrial Dysfunction,
Telomere Shortening, Senescence.

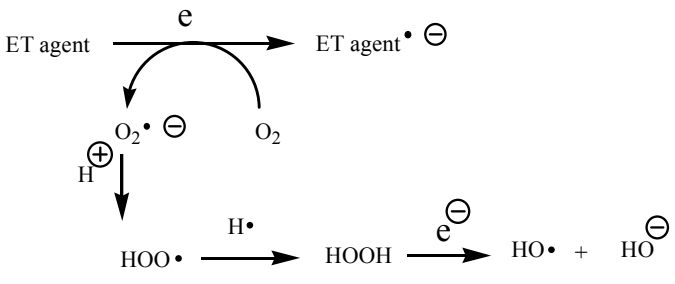
ABSTRACT

In addition to oxidative stress, several other mechanistic factors are involved with aging, namely, electron transfer, reactive oxygen species, and reactive nitrogen species. Evidence for beneficial effects of antioxidants provides support for the deleterious role of oxidative stress. Certain organs are importantly involved, such as heart, brain (Alzheimer's disease, dementia and Parkinson's disease), mitochondria, lung and prostate. Cancer is a significant contributing factor. Other aspects addressed are stem cells, protein oxidation, and telomeres.

Citation: Peter Kovacic and Ratnasamy Somanathan, 2017. "Various factors involving aging: Electron transfer, reactive oxygen species and oxidative stress", *International Journal of Current Research*, 9, (07), 53518-53528.

INTRODUCTION

This review deals with mechanism of aging from the standpoint of oxidative stress, electron transfer, reactive oxygen species, antioxidants, reactive nitrogen species, heart, brain, lung, prostate, mitochondria, and miscellaneous aspects. "The preponderance of bioactive substances, usually as the metabolites, incorporates ET functionalities. We believe these ET-metabolites play an important role in physiological responses. The main group includes quinones (or phenolic precursors), metal complexes (or complexors), aromatic nitro compounds (or reduced hydroxylamine and nitroso derivatives), and conjugated imines (or iminium species). Resultant redox cycling is illustrated in Scheme 1. In vivo redox cycling with oxygen can occur, giving rise to oxidative stress (OS) through generation of reactive oxygen species (ROS), such as hydrogen peroxide, hydroperoxides, alkyl peroxides, and diverse radicals (hydroxyl, alkoxyl, hydroperoxyl, and superoxide) (Scheme 1). Cellular and mitochondrial enzymes can also perform catalytically in the reduction of O_2.



Scheme 1. Redox cycling with superoxide and ROS formation

In some cases ET results in involvement with normal electrical effects (e.g., in respiration or neurochemistry). Generally, active entities possessing ET groups display reduction potentials in the physiologically responsive range, (i.e., more positive than about -0.5 V). Hence, ET in vivo can occur resulting in production of ROS which can be beneficial in cell signaling at low concentrations, but produce toxic results at high levels. Electron donors consist of phenols, N-heterocycles

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or disulfides in proteins which produce relatively stable radical cations. ET, ROS and OS have been increasingly implicated in the mode of action of drugs and toxins, (e.g., antiinfective agents (Kovacic & Becvar, 2000), anticancer drugs (Kovacic & Osuna, 2000), carcinogens (Kovacic & Jacintho, 2001a), reproductive toxins (Kovacic & Jacintho 2001b), nephrotoxins (Kovacic *et al*., 2002), hepatotoxins (Poli *et al*., 1989), cardiovascular toxins (Kovacic & Thurn, 2005), nerve toxins (Kovacic & Somanathan, 2005), mitochondrial toxins (Kovacic *et al*., 2005), abused drugs (Kovacic & Cooksy, 2005), pulmonary toxins (Kovacic & Somanathan, 2009), ototoxins (Kovacic & Somanathan, 2008), and various other categories (Halliwell & Gutteridge, 1999). There is a plethora of experime 2001antal evidence supporting the ET-ROS theoretical framework (Kovacic & Becvar, 2000; Kovacic & Jacintho, 2000a; Kovacic & Jacintho 2001b; Kovacic *et al*., 2002; Poli *et al*., 1989; Kovacic & Thurn, 2005; Kovacic & Somanathan, 2005; Kovacic*et al*. 2005; Kovacic & Cooksy, 2005; Kovacic & Somanathan, 2009; Kovacic & Somanathan, 2008; Halliwell & Gutteridge, 1999). This evidence includes generation of the common ROS, lipid peroxidation, degradation products of oxidation, depletion of AOs, effect of exogenous AOs, and DNA oxidation and cleavage products, as well as electrochemical data. This comprehensive, unifying mechanism is consistent with the frequent observation that many ET substances display a variety of activities (e.g., multiple-drug properties), as well as toxic effects. It is important to recognize that mode of action in the biodomain is often involved with many physiological actions and is multifaceted. In addition to the ET-ROS-OS approach, other aspects may pertain, such as, enzyme inhibition, allosteric effects, receptor binding, metabolism and physical factors. A specific example involves protein binding by quinones in which protein and nucleophiles, such as amino or thiol, effect conjugate addition" (Kovacic & Somanathan, 2010).

Origin and evolution of the theory

This aging theory was reviewed in 2009, fifty five years after the inception by Harman (Harman, 2009). Initially, there was considerable opposition, followed by increasing support in more recent years. Free radicals are widely generated in various parts of the body including mitochondria, the immune system, various redox enzymes, pollutants, drugs and many toxic substances. The final comment was "the work of more than 50 years has now established the validity and usefulness of the Free Radicals Theory of Aging." There was considerable research on the favorable effects of AOs which support the theory (Harman, 2000).

Free Radicals and Aging

Denham proposed the free radical theory of aging in based on damage to various body constituents by radicals (Halliwell & Gutteridge, 1999). The review presented the following:

a) ROS/RNS are generated by various means. There is damage to DNA, lipids and protein. AO defenses do not protect completely.
b) ROS/RNS formation may benefit in the short term, but may lessen with age.
c) Tissue degeneration with age can generate enhanced ROS/RNS. For example, old rats form more superoxide than young ones, pointing to greater leakage of mitochondrial electrons followed by superoxide production with aging.
d) Larger animals consume less O_2 than do smaller ones resulting in larger life span. There is a lower ROS burden.
e) Changes in O_2 consumption resulting in alteration of ROS levels can affect life span.
f) Lowered O_2 consumption by queen bees who do not fly most of their lives could explain why they live many times longer than the flying worker bees.
g) Mitochondrial DNA undergoes rapid mutations partly due to oxidative damage leading to higher levels of 8-OHdG.
h) Data indicate that longer-lived species possess superior AO protection than shorter-lived ones.
i) A slower rate of ROS generation from mitochondria may be related to increased age.
j) Senescense can be induced by H_2O_2 (an ROS) treatment apparently associated with increased levels of 8-OHdG.
k) Caloric restriction is related to less oxidative damage to DNA, lipids and protein associated with decreased superoxide production.

Studies with added AOs have produced unexpected results with no or little increase in longevity. It is difficult to interpret the data.

Reactive oxygen species, oxidative stress and antioxidants

Aging is an extremely complex and multifaceted process that proceeds to the gradual deterioration of the various physiological functions in the organs of the body. In recent years, a large body of literature has emerged documenting the link between ROS, reactive nitrogen species (RNS), antioxidants (AOs) and aging (Polijsak, Milisav, 2013; Roberts & Fulop, 2014; Stojilković *et al*., 2014; Poljsak *et al*., 2013; Yadev *et al*., 2013; . Rahman *et al*., 2012; Germs & de la Gurdia, 2012; Cui *et al*., 2012; Ladiges *et al*., 2010; Goto, Radák, 2010; Pamplona, 2008; Olinski *et al*., 2007; de Magalhães & Church, 2006; . Junqueira *et al*., 2004; Stadtman, 2004; Bokova *et al*., 2004; Turrens, 2003; Wei & Lee, 2002; Cadenas & Davies, 2000).

Antioxidants and aging

Excessive ROS formation induces OS, which plays a large role in the disease process and natural aging. It is well established that free radicals (·OH, $\cdot O_2$, ·OOH etc.) damage is linked to the formation of many degenerative diseases, including cancer, cardiovascular diseases, neurodegenerative diseases, Alzheimer's, Parkinson's, Huntington's and aging (Poljsak & Milisav, 2013; Stojiković *et al*., 2014; Olinski *et al*., 2007; Cadenas & Davis, 2000; . Nordberg, & Arnér, 2001; Valko *et al*., 2007; Seifried *et al*., 2007; Uttara *et al*., 2009; Wei & Lee, 2002; Guerra-Araiza *et al*., 2013; Kovacic *et al*., 2015; Kovacic & Somanathan, 2006). Cells have antioxidants that scavenge excessive ROS by AGs, such as superoxide dismutase, catalase, glutathione and glutathione-related enzymes, thioredoxin, vitamin E, lipoic acid, N-acetyl-L-cysteine and ubiquinones. Although historically viewed as harmful, recent evidence suggests that ROS function as important physiological regulators of intracellular signaling pathways and the induction of a mutagenic response (see free radical section). Excessive production of ROS, ultimately leads to apoptosis, necrosis and loss of cells. A balance between

oxidants and antioxidants in intracellular systems is vital for cell function, regulation, adaptation and growth. Aging is a process which starts after maturity, when most of the physiological functions related to the heart, lungs, kidney, sexual hormones, skin wrinkling, CNS and brain functions show signs of decline. It is believed that the aging involves complex and interrelated factors, including oxidative stress-induced protein and DNA damage in conjunction with insufficient DNA damage repair, as well as genetic instability of mitochondrial and nuclear genomes (Polijsak & Milisav, 2013; Fontana& Klein, 2007), increased adipokine and cytokine production (Davis, 1995), alteration of fatty acid metabolism, tissue insulin resistance (Martin, 1987), accumulation of glycation end products (Kovacic & Somanathan, 2011; Martin *et al*., 1996), alterations in the sympathetic and neuroendocrine systems (Gilica *et al*., 2007), loss of post-mitotic cells, and deterioration in structure and function of cell neurons, and muscles in all tissues and organs (Polijsak & Milisav, 2013).

Theoretical aspects

There are many theories which help to elucidate the process of ageing, such as free radical, oxidative stress, mitochondrial, telomere shortening, end glycation product, protein damage, and DNA damage that have evolved over the years (Fig.1). None of these theories alone can explain all details of ageing (Polijsak & Milisav, 2013). Further, there are specific aging genes of which, almost 7,000 play a role in senescence of an aging person. However, reactive oxygen species and oxidative stress have been a common factor in most of these theories, in keeping with our hypothesis that ROS-OS-ET is a unifying mechanism to explain many of the diseases and aging encountered in living organisms (see Introduction).

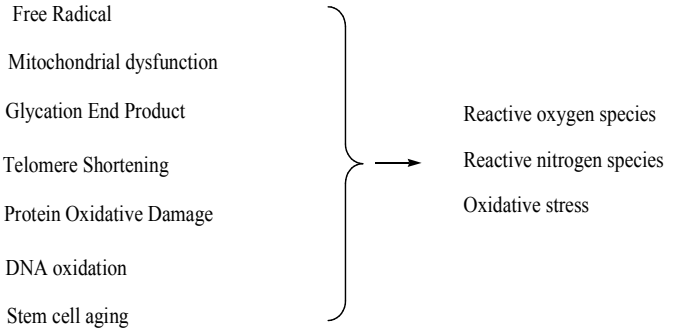


Fig.1. Various theories on aging

Free radicals, oxidative stress and mitochondrial dysfunction

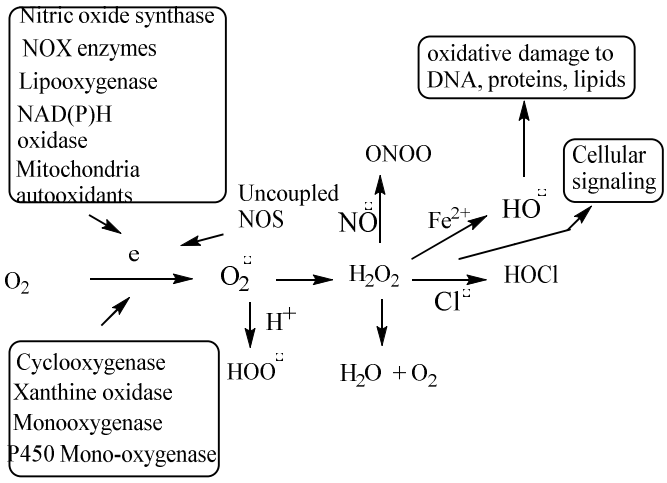
Harman proposed the free radical theory of aging in the 1950s, with the accumulating evidence of reactive oxygen species, mitochondrial dysfunction and oxidative stress being the main causes of aging. A large body of evidence accumulated over the years suggesting a strong link between aging and ROS-OS. Studies have shown a correlation between longevity and the rate of cellular damage.

Reactive oxygen species can be classified into two groups: free oxygen radicals and non-radical ROS (Table 1). Among these, superoxide, hydrogen peroxide and hydroxyl radicals are the most potent and well studied species.

Table 1. Reactive oxygen and nitrogen species

Radical ROS		Non-radical ROS	
Superoxide	$O_2^{\bullet -}$	Hydrogen peroxide	H_2O_2
Hydroxyl radical	$HO^{\bullet}$	Singlet oxygen	O_2
Nitric oxide	$NO^{\bullet}$	Ozone	O_3
Organic radicals	$R^{\bullet}$	Hypochlorous acid	HOCl
Peroxyl radicals	$ROO^{\bullet}$	Organic hydroperoxides	ROOH
Alkoxy radicals	$RO^{\bullet}$	Peroxynitrite	ONO^-
Nitrogen dioxide	$NO_2^{\bullet}$	Nitrous acid	HNO_2

A variety of enzymatic and non-enzymatic sources of ROS exists in the biological system. Enzymes within the cell are primary sources of ROS/RNS. Superoxide is produced by one electron reduction of oxygen by several enzymes, such as NAD(P)H oxidase, xanthine oxidase and cytochrome P450 within the cell. In addition to these, a number of external mediators also contribute to the ROS generation, such as ionizing radiation. Heavy metals, like Hg, Pb, Cd, Cr, and Cu, metal complexes, nanoparticles, cigarette smoke, pollutants from automobiles, fossil burning furnaces, various drugs and certain types of other chemical compounds (Scheme 1) play a role (Gilica *et al*., 2007; Halliwell, 2001; Krumova & Cosa, 2016).



Scheme 1. Generation of ROS

In mitochondria, superoxide ROS is produced as a natural by-product of electron transport chain activity. The superoxide leaks through the mitochondrial permeability transition pore in the outer membrane into the cytoplasm, where it is converted into hydrogen peroxide by MnSOD or in the cytosol by Cu/ZnSOD. The diffusible hydrogen peroxide also serves as a second messenger, and may cross cellular membranes through members of the aquaporin family (Halliwell, 2001; Krumova & Cosa, 2016; Turrens, 2003). The superoxide created by the mitochondrial metabolized oxygen is converted into hydrogen peroxide, hydroxyl radical, peroxy radical and other radicals capable of damaging proteins, lipids, mtDNA, neurons, brain tissue, cardiovascular tissue, endothelial tissue and skeletal tissue. Since mitochondria are the major source of ROS in mammalian cells, the closest attack also takes place at the

mitochondrial DNA (mtDNA). Aging is a consequence of this mitochondrial dysfunction and other actions due to the ROS formation, leading to various age related diseases including cancer, Alzheimer's, Parkinson's and other neurological disorders, wherein is supported by various reports (Turrens, 2003; Sanz & Stefanatos, 2008; Dai *et al*., 2014; Bánhegyi & Sümegi, 2014; Krzeszowiak & markiewicz-Górka, 2014; Piotrowska & Bartnik, 2014; Indo et. al2015; Springo *et al*., 2015; Li *et al*., 2014; Conti *et al*., 2015; Haddadi *et al*., 2014: Patel *et al*., 2014; Ladiges *et al*., 2010; Liou & Storz, 2010; Sullivan & Chandel, 2014; Loeb *et al*., 2005; Balaban *et al*., 2005; Barja, 2004; Junqueira*et al*., 2004; Lin & Beal, 2006; Hirai *et al*., 2001). Studies have shown that 8-oxo-dG, a common oxidized product of DNA is found in higher levels in the mtDNA than in nuclear DNA (Cui *et al*., 2012). The accumulation of oxidative DNA damage products, e.g., 8-oxo-dG from mtDNA, contributes to the aging process (Cui *et al*., 2012; Maynard *et al*., 2009; Capel *et al*., 2005). Studies with mice and fly models show that reduced free radical production increased life span (Cui *et al*., 2012). *C.elegans* resistant to OS have a longer life span, whereas mice lacking antioxidant enzyme SOD exhibit a shorter life span (Cui *et al*., 2012). Mice that lack DNA repair enzymes, such as 8-oxaguanineglycosylase and Muty homolog 1, have shorter life spans (Cui *et al*., 2012). Mitochondrial ROS were shown to regulate the NF-kB pathway, together with age–related inflammatory activation of endothelium, which leads to vascular dysfunction and oxidative stress-related diseases (Li *et al*., 2015; Zinovkin *et al*., 2014). Clinical studies showed mitochondrial ROS-induced cataract in aging eye (Babizhayev and Yegorov, 2016). A study provides epidemiological evidence supporting free radical/oxidative stress using derivatives of reactive oxygen species metabolites and total thiols as biomarkers (Schöttker *et al*., 2015). Dietary restrictions decrease mitochondrial ROS production, leading to animal longevity (Pamplona and Barja, 2007). Lowering methionine levels in tissue proteins controls mitochondrial oxidative stress and increases the longevity of mammals and birds (Pamplona and Barja, 2006). Superoxide (CuZn) dismutase deficiency causes accelerated vascular aging process (Chen and Chen, 2006). ROS have historically been viewed as toxic metabolic byproducts and have been identified in many physiological dysfunctions and pathologies, such as atherosclerosis, diabetes, cancer, neurodegeneration, and aging. More recent work, however, indicates ROS are important intermediates in cellular signaling pathways, initiating signaling in a broad variety of cellular processes, such as proliferation and survival (MAP kinases, P13 kinase, PTEN, and protein tyrosine phosphatases, ROS homeostasis, antioxidant gene regulation, mitochondrial oxidative stress, apoptosis and aging (Thannickal and Fanburg, 2000; Hamanaka and Chandel, 2010; Marchi *et al*., 2012; Yan, 2014; Ludovico and Burhans, 2014; Liochev, 2013; Labunskyy and Gladyshev, 2013; Ray *et al*., 2012; Collins *et al*., 2012; Back *et al*., 2012).

Stem cell and reactive oxygen species

Stem cells, which are capable of self-renewal and differentiation, are essential for the normal homeostatic maintenance and repair of tissue throughout the life span of an organism. Studies indicate self-renewal ability of adult stem cells declines with advancing age, suggesting that stem cell function plays a central role in aging. Hypoxia and low ROS play an important role in regulating stem and progenitor cell function in various physiological and pathological responses (Maraldi *et al*., 2015; Bigarella *et al*., 2014; Shyh-Chang *et al*., 2013). Studies deal with ROS mechanism, metabolism and aging in stem cells (Bigarella *et al*., 2014; Sharpless & DePinho, 2007). Aging increases the susceptibility of mesenchymal stem cells to ROS and impairs their therapeutic transplantation for myocardial infarction (Atashi *et al*., 2014). A similar report deals with ROS in mesenchymal stem cell aging and its implication in lung diseases (Yang *et al*., 2015). Genetic studies of mice deficient in gene implicated in ROS regulation have demonstrated that elevated levels of ROS within the stem cell compartments lead to a rapid decline in stem cell self-renewal (Ito, 2004; Mantel, 2012; Rossi, 2007). Accelerating neuronal aging in *in vitro* model brain stem cell disorders was shown to involve ROS (Campos *et al*., 2014).

Protein oxidation

It is known for a long time that aging is associated with the accumulation of altered forms of a number of enzymes (Rohtstein, 1984). Modified or oxidized proteins are dysfunctional as enzymes or as structural proteins. Oxidative attack of the polypeptide backbone is initiated by the ROS and RNS dependent abstraction of the α-hydrogen atom of the amino acid residue to form a carbon-centered radical. All amino acid residues of proteins are susceptible to oxidation by ROS and RNS radicals (Berlett and Stadtman, 2013). Protein oxidative modifications can be classified into two types, irreversible oxidation and reversible oxidation (Cai and Yan, 2013). Studies have shown the detrimental effects of protein oxidation in aging (Stadtman, 2001; Stadtman, 2006). An investigation showed the effects of both irreversible and reversible protein oxidation products in health and disease (Cai and Yan, 2013). Several other investigations relate to protein oxidation and aging (Baraibar *et al*., 2012; Shringapure and Davis, 2002; Höhn *et al*., 2013; Sitte *et al*., 2000; Sitte *et al*., 2000; Friguet, 2006).

Telomere shortening, senescence, ROS and aging theory

Telomeres, nucleoprotein structures located at the ends of chromosomes, are subjected to shortening at each cycle of cell division. Telomeres prevent chromosome ends from being recognized as double-strand breaks and protect them from end to end fusion and degradation. Unlike stem cells, telomeres in somatic cells shorten with each division leading to cellular senescence (aging). The enzyme telomerase is involved in telomere stability by synthesizing a new copy of the repeat by using its RNA template. Oxidative DNA damage can lead to dysfunctional telomere. DNA damaged senescence cells were found to contain 30% more oxidative modified guanine in their DNA. Evidence points to oxidative modifications and shortening by ROS leading to aging of the somatic cells (Kawanishi and Oikawa, 2004; Stte *et al*., 1998; Kamsler. Kamsler *et al*., 2001; Tchirkov and Lansdorp, 2003; Duan *et al*., 2005; Blasco, 2005; Xin and Broccoli, 2004; Hausmann *et al*., 2003; Camisi, 2005; Jeyapalan & Sedivy, 2008; Collado *et al*., 2007). Fig. 2 summarizes the role of ROS/RNS in aging.

Cardiovascular System

Among the most numerous causes of mortality in the USA are heart attacks (Kovacic and Thurn, 2005). Deleterious effects include arrhythmia, causing cell injury resulting in necrosis or myocyte death, and necrotizing injury.

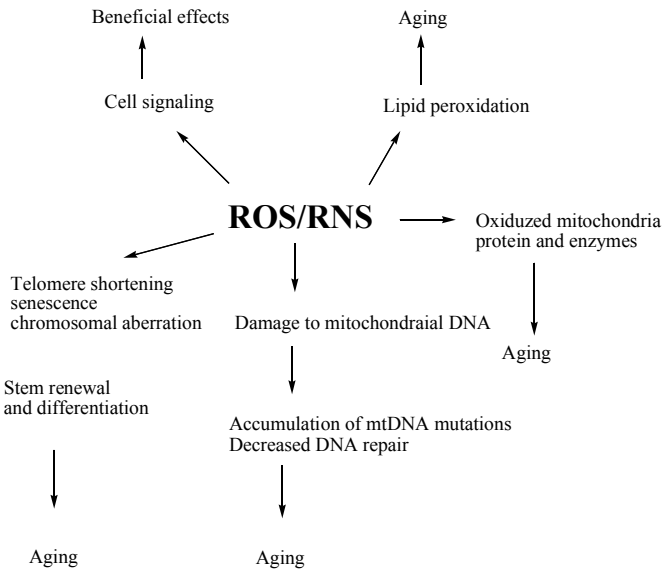


Fig.2. ROS/RNS in aging

The review discusses involvement of ET-ROS-OS-AO. The liporfuscin test showed enhanced OS with aging after 20 years. The review deals with radical species in cardiac tissue injury. ROS formation is associated with cardiovascular toxins. The heart is characterized by a number of adverse factors, including high oxygen consumption, abundance of mitochondria and deficiency of AO defenses. There are large number of substances harmful to the heart that fit the oxidative stress theory. Among these are medicines, such as, anthracyclines, quinolones, gentamycin, methyldopa, and amphotericin B. Harmful abused drugs include alcohol, cocaine, tobacco, nicotine, N-nitrosamines, polynuclear aromatic hydrocarbons, amphetamines and MPTP. The cardiovascular system is adversely affected by a significant number of metal compounds, mainly those of Cd, Co, Pb, Mn, Ni, V, As, Cr, Cu, Fe and Hg. The metals generally exhibit reduction potentials favorable for ET leading to ROS. The adverse effects are alleviated by AOs of various types. Included in the pesticides and herbicides categories are lindane, paraquat, organophophates and carbon disulfide. Toxic industrial chemicals include haloalkanes, alkenes, acrolein and allylamines. In addition, there are large numbers of miscellaneous compounds, e.g., catecholamines, endotoxin, alloxan, nitric oxide, PCBs,dioxin, phenylhydrazines, sulfur dioxide and dinitrotoluene. AOs that have exhibited effectiveness in decreasing risk of mortality from heart disease include flavonoids, vitamin E, selenium, vitamin C, probucole, ubiquinol, cysteine, SOD, catalase and GSH.

Alzheimer's Disease

This illness (AD) is characterized by three conditions, namely, senile plaque (SP), neurofibulary tangles and synapse loss (Butterfield, 2003). Clinical manifestations include loss of memory, speech, cognition and normal behavior. AD is one of the main causes of aging and death. Research indicates that the main component of SP, namely amyloid βpeptide (Aβ) is central to the pathological condition, including OS. The AD brain is under intense OS as shown by protein oxidation. Lipid peroxidation, ROS formation, advanced glycation end products and DNA oxidation. The generation of superoxide and NO leads to peroxynitrite, a neurotoxic species, lipid peroxidation, resulting from radicals associated with Aβ, can damage membrane proteins. Another product of lipid peroxidation is the toxic 4-hydroxy-2-nonenal (HNE). Protein oxidation is caused by Aβ. The three major ways of introducing carbonyl groups into protein by OS are peptide breakdown scission by radicals, selective oxidation on amino acid side chains and protein modification by alkenals. Lipid peroxidation is caused by an Aβ-induced lipid peroxidation in the AD brain. Studies indicate that a therapeutic strategy is to block OS associated with Aβ using brain accessible AOs.

Dementia

Dementia is a complex brain disorder composed mainly of AD, Lewy bodies (Mao, 2013), and vascular types (Bennett, 2009) involving OS. Other factors are endothelial dysfunction, in addition to neuronal cell death and damage. The condition is characterized by increase in oxidative DNA damage, including formation of 8-oxyguanine (Gackowski *et al*., 2008). Resveratrol, an AO, anti-inflammatory and anti-carcinogen, exhibits beneficial effects in dementia (Ma *et al*., 2013). A decrease in AO levels and increase in oxidative damage are apparently involved in the pathophysiology associated with diabetes-related dementia (Hatanka *et al*., 2015). Oxidative damage is an early indicator of frontotemporal dementia (Gerst *et al*., 1999). The AO S-alkyl cystiene alleviates OS related to cognitive impairment and neurodegeneration in mice with Alzheimer's dementia (Khan *et al*., 2011). Selenium compound protected against free radical deterioration of cognitive functions and neurobehavioral, in addition to memory loss (Chiapinotto*et al*., 2015). SOD activity was protected. OS may be a feature of cognitive impairment and AD (Cervellati *et al*., 2014). There is discussion of OS with involvement in dementia.

Parkinson's Disease

Parkinsonson's disease (PD) usually occurs after 65 and slowly progresses until death (Adams *et al*., 2001). The disease is caused by the death of dopaminergic neurons in the brain. OS is involved in the process of killing these cells, entailing ROS. Mitochondrial dysfunction, which generates superoxide, has been implicated in PD. Dopaminergic neurons die by apoptosis in a process involving OS. ROS abstract hydrogen from DNA forming radicals that fragment, leading to apoptosis. Tyrosine hydroxlase can give rise to ROS in a redox mechanism. Dopamine may be oxidized to form ROS. 3,4-Dihydroxyphenylacetaldehyde is also involved in the generation of ROS. There are many mechanisms for ROS generation in dopaminergic neurons, none of which should be ignored. Monoamine oxidase, may also be important in PD.

Prostate

Prostate cancer is the most common type and is the second main cause of death from cancer involving USA males (Sikha, 2003). Various models of action play a role, such as genetics and OS, the latter being supported by extensive evidence. The ROS involved are produced by carcinogens, illness, infection, inflammation, aging, nutrients and pollutants. The ET-ROS-OS mechanism is believed to be involved. Also participating are RNS, such as NO and peroxynitrite.

Lung

The lung is another organ which is involved in aging and death. A recent review addresses pulmonary toxicity based on the unifying theme of ET-ROS-OS (Kovacic and Somanathan,

2009). The pulmonary system is a main target for toxicity. In the industrial age, there has been a substantial increase in atmospheric pollutants. In lung tissues, many adverse effects result from exposure to lung pollutants that fit into the unifying theme of ET-ROS-OS. More familiar examples include the following: ozone, SO_2, chlorine, benzene, chloroform, carbon tetrachloride, pentachlorophenol, anesthetics, metals and metal compounds, particulates, asbestos, silica, tobacco (N-nitrosoamines), cocaine, nitroaromatics (Kovacic and Cooksy. 2010) and diacetyls (Kovacic and Somanathan, 2014). Exposure to pollutants results in various illnesses related to aging, including asthma, COPD and cancers (Kovacic and Somanathan, 2009).

Mitochondria

There exists considerable literature linking mitochondria to aging, much of which relates to the unifying theory of ETR-ROS-OS. Some of the reports are present in other sections. This portion is mostly concerned with more recent materials. ROS, generated by mitochondria or other sites, damage various components including the mitochondria, and induce harmful degradation of body components (Bonomini *et al*., 2015). Such toxic manifestations make up a significant portion of aging. The review addresses metabolic syndrome in connection with accelerated senescence. Two items are closely related to species longevity, namely rate of ROS formation by mitochondria and degrees of unsaturated fatty acids in tissue (Barja, 2014). Both are low in longevity. Other factors involved are also treated. Mitochondrial ROS importantly participate in the health span of many essential body organs, as discussed in other sections of the present review (Dai *et al*., 2014). There is a related article (Kong, 2014). ROS at a low, non-toxic concentration can operate as cell signaling agents that protect against damaging events (Liu *et al*., 2014). Also, peroxiamine, closely related to mitochondria, appear to play a role in longevity. Events following oxidative damage induce inflammation, followed by apoptosis (Venkatarama *et al*., 2013). OS related to the cardiovascular and central nervous systems is discussed with emphasis on aging-related diseases. A review discusses the free radical theory from various perspectives, including mitochondrial pathways involving apoptosis that causes subsequent functional tissue alterations (Ivanova and Yankova, 2013). Included is discussion of delay in aging by diet or drug therapy. A 2013 review presents an updated view of the mitochondrial free radical theory (Barja, 2013). Key aspects are emphasized. The two general characteristics responsible for animal longevity appear to be low rate of endogenous damage and macromolecular tissue makeup that is very resistant to oxidative damage.

Cancer

Cancer is one of the main factors involved in shortening the length of life. After a continuing rise in cancer death rates, there has been a steady decline since 1990 (Newcott, 1916). The illness is multifaceted making for difficulty in prevention and treatment with a multitude of targets involved. In relation to mode of action, various factors have been discussed, including genes, DNA, mutagenesis, estrogens and inflammation. This review deals with the unifying mechanism involving ET-ROS-OS-AO (Kovacic and Jacintho, 2001a). The Introduction provides more detailed information. Carcinogenic ET quinones are represented by adriamycin, daunomycin, pyrene quinones and estrogen quinone. The requisite quinone is frequently generated from metabolic precursors, such as benzene, phenols (catechols), hydroquinones, biphenyls and polynuclear aromatic hydrocarbons. Other examples of ET carcinogens are aromatic benzenoid and heterocyclic nitro compounds, such as nitropyrene and 4-nitroquinoline-N-oxide, aromatic pri-amines (benzenoid and heterocyclic), such as benzidine, imidazolquinoxalines and imidazopyridines. Another carcinogenic category includes agents, which alkylate macromolecules, primarily DNA. These substances generate ROS, followed by oxidation of DNA. There is scarcity of mechanistic details. There are other N-containing compounds that are carcinogens, such as hydrazines and N-nitroso compounds. Several studies indicate involvement of ROS. In relation to the various carcinogens, the supporting evidence has been characterized as overwhelming. However, AO research with humans revealed little or no protective effect which proves to be difficult to rationalize.

Other Literature

Two types of hereditary diseases are discussed, namely those involving chromosome instability, e.g., Fanconi's, and genotypis illnesses, such as Dounis syndrome and cystic fibrosis (Korkina *et al*., 1998). All are associated with cancers and premature aging due to OS. Chromosome instability in Fanconi's anemia is related to DNA repair defect caused by ROS. The relation of high expectancy has been demonstrated for various factors, such as ROS generation in mitochondria, modifications of mitochondrial DNA and involvement of polyunsaturated fatty acids (Dubinina and Pustygina, 2007). OS plays a role, e.g., in various neural disorders, An important aspect is oxidized proteins, as in Alzheimer's, Parkinson's and Lou Gherig's diseases. A report deals with free radicals and mitochondrial aging (Jendryczko, M. Drózdz, 1989). The factors discussed include metabolic rate, AO addition and limited caloric intake. There is a related article (Bobyrev, 1989). A review treats mitochondrial and other sources of radical entities (Arutiunian and Kozina, 2009). Relation of AO enzyme activity and life expectancy isdiscussed. Data deal with AO compounds and protection against aging. Later a "vicious cycle" theory was proposed in which ROS from respiration impair mitochondrial DNA (Szarka *et al*., 2014). Generation of the mutations is accelerated by the "vicious cycle" which is involved in accelerated aging. An article presents OS as a universal cause for aging in humans, yeast and bacteria (Ksiazek, 2010). SOD and superoxide are the center of attention in the free radical theory of aging (Gusev and Panchenko, 1982). There is discussion of cell division and differentiation. Reduced efficiency of the repair process in damaged cells and OS are discussed in an article (Michalak *et al*., 2014). Factors involved are oxidative damage to molecules, such as proteins, lipids and nucleic acids. DNA damage is an important focus with emphasis on mutation. Lipid peroxidation and repair systems are treated. Evidence indicates that ROS play a role in pathogenesis of the skin (Kozina *et al*., 2012). The role of ROS and AOs is addressed. A focus is on damage by exposure to UV light.

Conclusion

In conclusion oxidative stress and several other mechanistic factors are involved with aging, namely, electron transfer and reactive oxygen species, and reactive nitrogen species. Evidence for beneficial effects of antioxidants provides

support for the deleterious role of oxidative stress. Certain organs are importantly involved, such as heart, brain (Alzheimer's disease, dementia and Parkinson's disease), mitochondria, lung and prostate, oxidative stress in these organs contribute to aging. Cancer is a significant contributing factor. Other aspects addressed are stem cells, protein oxidation, and telomeres and they all contribute to aging.

Acknowledgement

Editorial assistance by Thelma Chavez is acknowledged.

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