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Age-associated neurodegeneration and oxidative damage to lipids, proteins and DNA

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ABSTRACT

Lipids, proteins and DNA in the central nervous system have a high sensitivity to oxidative stress. Reactive oxygen species (ROS)-induced damage increases with aging, especially in the last quarter of the life span. The so called base level of oxidative modification of lipids could be important to cell signaling, and membrane remodeling, but the ROS-mediated post translation modifications of proteins could be important to the homeostasis of protein turnover. Low levels of 8-oxo-7,8-dihydroguanine (8-oxoG) might be necessary for transcription. A high level of accumulation of lipid peroxidation, oxidative protein damage or 8-oxoG, on the other hand, accelerates the progress of aging and neurodegenerative diseases. Therefore, agents that induce the activity of repair enzymes, such as Ca(2$^+$)-independent phospholipase A(2) (iPLA(2)beta), methionine sulfoxide reductase, and 8-oxoguanine DNA glycosylase, or the activity of enzymes that could prevent the accumulation of oxidized, toxic proteins, such as proteasome, Lon protease, neprilysin or insulin degrading enzyme, may act as potential therapeutic tools to slow the aging process and the progress of neurodegenerative diseases.

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1. Introduction

Respiration can release up to 2870 kJ from the complete oxidation of 1 mol glucose, whereas anaerobic metabolism results in just 197 kJ. The highly efficient aerobic metabolism burns substrates without direct substrate–oxygen interaction, but it utilizes oxygen as a final electron acceptor. During this process, most probably not by coincidence but because of the physiological means, the electron chain releases reactive oxygen intermediates. One of the important characteristics of these reactive oxygen species (ROS) is that their outermost orbit contains an unpaired electron that has an independent existence.

Some of the ROS, including nitric oxide, but mostly the less reactive hydrogen peroxide, can cross membranes and act as activators for vital physiological processes. The redox signaling is important to inflammation via the activation of NF-kB and AP1 (Bowie and O'Neill, 2000; Sen and Packer, 1996), vascularization via HIF-1–VEGF activation (Liu et al., 2006), mitochondrial biogenesis (Schroeder et al., 2007; Strobel et al., 2011), or different metabolic adaptations via SIRT1 (Puca et al., 2010).

Moreover, it appears that ROS are involved in neurogenesis, since neuronal precursor cells exhibit about four times higher ROS levels than other cell types, and the concentration of ROS which is dependent on the density of precursor cells is associated with the rate of proliferation (Limoli et al., 2004). Furthermore it has been suggested that ROS are important messengers and activate, up to a certain concentration, the self-renewal multipotent neural progenitors and neurogenesis

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via P13K/Akt signaling (Le Belle et al., 2011). Generally it appears that elevated ROS levels (excluding the very reactive ones, like hydroxyl radical) can stimulate a variety of physiological functions. However, after reaching a critical level, ROS can jeopardize cell function and fate. Thus, the effects of ROS on biological systems can be described by the hormetic curve (Radak et al., 2005, 2008). It seems to be indisputable that ROS, above a cell dependent tolerance level, readily induce the oxidative modification of macromolecules, and this process is generally referred to as oxidative damage.

Brain is an organ very sensitive to oxidative stress and this is partly due to the high metabolic rate and the large amount of iron and copper found in the organ. These interact with the diffusible hydrogen peroxide and result in the generation of the extremely reactive hydroxyl radical that yields damage to proteins, lipids and DNA (Halliwell, 2001; Nagy, 2001). Hydrogen peroxide is generated by a number of systems, including reactions catalyzed by monoamine oxidase A and B with a described location of neuronal and glial mitochondrial membranes (Gershon et al., 1990). Besides the possible iron–hydrogen peroxide interactions, Ca^{++}-associated ROS generation is also a potent source of ROS in the brain. Both inhibition and activation of neurons activates Ca^{++}-traffic, and the excess of glutamate could result in large increases in ROS production (Butterfield, 2002; Chinopoulos and Adam-Vizi, 2006). Neuronal membranes are packed with phospholipids containing polyunsaturated fatty acid esters, which are very sensitive to ROS attack, causing a chain reaction which generates lipid radicals and extensive membrane damage. NADPH oxidases are potent cellular generators of superoxide including neurons and glias (Lambeth, 2007). NADPH oxidase ROS generation can be influenced by free fatty acids especially mono and polyunsaturated long chain fatty acids, which could increase ROS production (Schonfeld and Wojtczak, 2008). Despite the fact that brain is well protected by the blood–brain barrier, it is important to note that it cannot provide full protection against circulating inflammatory agents that can generate radicals in the brain (Farkas et al., 2006).

It is well established that oxidative stress is closely linked to the pathology of a variety of neurodegenerative diseases, including age-associated disorders (Jellinger, 2009; Koudinov et al., 2009; Radak et al., 2010). Due to this reactivity and short lifespan, the direct detection of ROS is difficult, and hence, the amount is often judged from the alteration of antioxidant status or the accumulation of relatively stable products of lipid, protein and DNA interactions. However, the levels of oxidative damage, besides the concentration and reactivity of ROS, are also influenced by the activity of the repair systems.

The levels of oxidative modification of lipids, proteins and DNA are generally used as markers of oxidative damage, which is increased with the neuropathology of aging, and in some cases it has even been suggested to be a causative factor of the progress of specific diseases (Esiri, 2007; Head, 2009; Martin, 2008). In the present review the reasons and consequences of the accumulation of oxidative damage in age-associated diseases, with a special focus on the repair process, have been evaluated. The activation of repair processes could serve as a potential therapeutic tool to attenuate the progress of certain diseases.

2. Lipid peroxidation and neurodegenerative diseases

Cellular membranes that provide structural integrity for cells are composed of a variety of phospholipids, cholesterol, cholesterol esters and fatty acids and a variety of proteins that have key roles for specific cellular functions (Catala, 2009). Cholesterol is an important regulator of the complete lipid architecture including the assembly of myelin structure (Saher et al., 2005). In addition, phospholipids could serve as precursors for signaling such as arachidonic acids (ArAc), docosahexaenoic acid (DHA) among others, which at low concentration can regulate signal transduction, gene expression, and cell proliferation (Farooqui and Horrocks, 2006). ArAc is generated by phospholipase A2 and it is metabolized by cyclooxygenase, and lipoxygenase to bioactive eicosanoids (Fig. 1).

Mammalian cells contain 1500–2000 lipid species. Brain is particularly important in lipid metabolism, since this organ has the highest concentration of lipids, excluding adipose tissue in mammalian bodies. Indeed, supplementation of certain polyunsaturated fatty acids can attenuate the development of gliomas (Kyritsis et al., 2011), protect against the damage of traumatic brain injury (Mills et al., 2011; Wu et al., 2004a), and improve synaptic plasticity (Wu et al., 2008). However, a high fat diet containing saturated fatty acids could impair synaptic plasticity via cyclic AMP-response element-binding protein (CREB), synapsin 1 systems (Wu et al., 2004b). Thus, lipids are important modulators of brain physiology that are also targets of ROS.

Radicals, especially hydroxyl, alkoxyl, and peroxyl, can abstract a labile H atom from the methylene group of polyunsaturated fatty acids, generating carbon-centered free radicals. Thus, the initial reaction of hydroxyl radical with fatty acids produces a lipid radical which, with the reaction of oxygen, results in the lipid peroxyl radical, which further can react with fatty acids to produce lipid hydroperoxide. This chain reaction could significantly alter the structure of membranes and other lipids, resulting in altered fluidity, permeability, transport and metabolic processes. Fatty acid peroxides can give rise to a variety of aldehydes. Among the generated aldehydes, 4-hydroxy-2-nonenal (HNE) is considered to be one of the most toxic that causes extensive damage and results in apoptosis (Dubinina and Dadali, 2010). HNE can be generated from ArAc or linoleic acid after being attacked by peroxides and due to the lipophilic characteristics of HNE it can easily be associated with membranes. However, HNE is also capable of disintegrating membranes and is able to travel between cell components. HNE interacts with membranes and a wide array of amino acids residues that in receptors, chaperones, electron transport chain proteins and oxidative damage repairing proteins (Dubinina and Dadali, 2010; Farooqui and Horrocks, 2006).

Accumulation of beta amyloid (Aβ) in neurofibrillary plaques is a pathological characteristic of Alzheimer's disease (AD) and is associated with neuronal death. Moreover, addition of Aβ has been shown to cause the generation of HNE (Mark et al.,

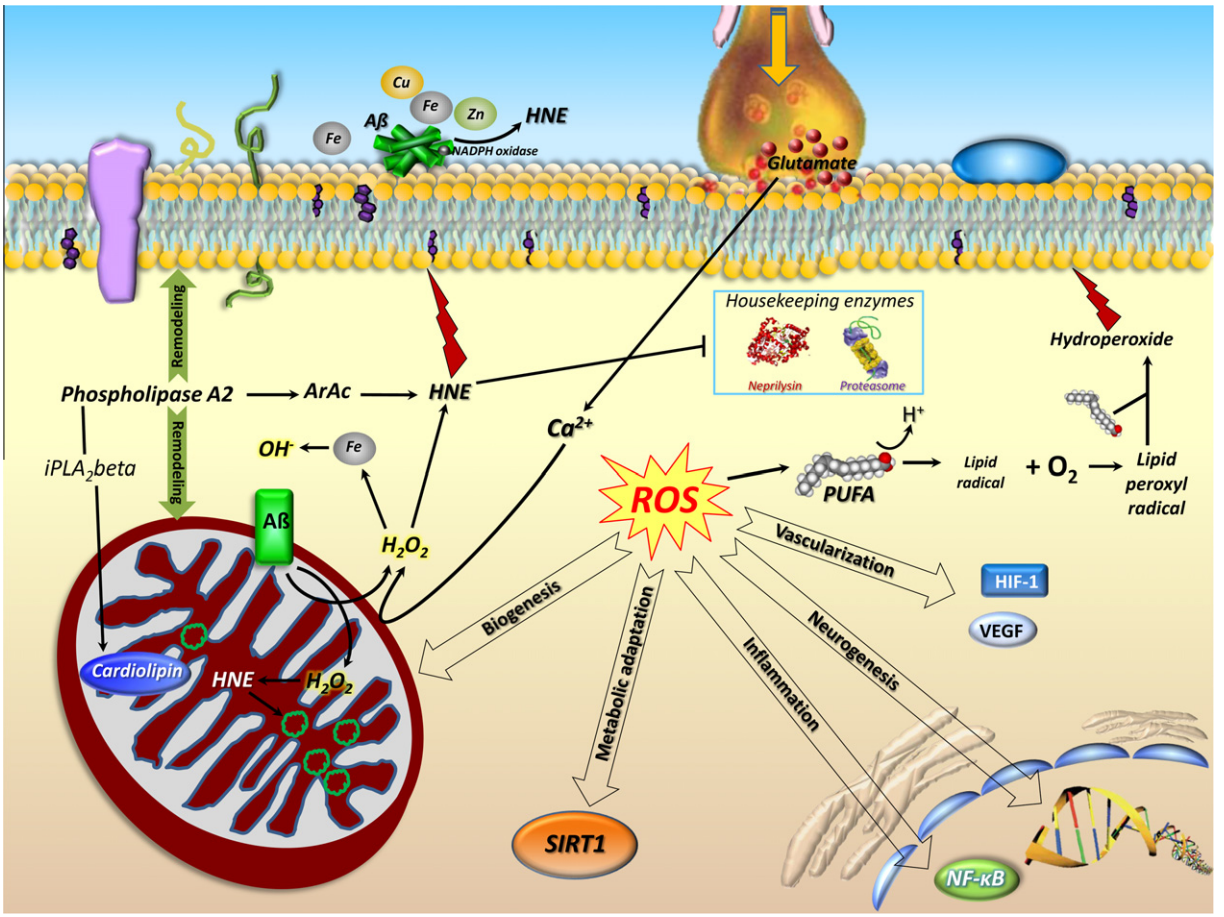

Fig. 1. Involvement of ROS in membrane lipids in pathophysiology of cells. ROS gives rise to lipid peroxides in the cell membrane resulting in either the chain reaction of lipid peroxidation or generation of aldehydes such as HNE that are harmful to cellular functions via Ca^{2+} signaling, leading to pathologies like inflammation. Beneficial sides of ROS are, if modest, roles in mitochondrial biogenesis, neurogenesis, metabolic adaptation, etc.

1997), and hence a Aβ is a potent generator of lipid peroxidation and acts as a neurotoxin. Microglial NADPH oxidase activation has been suggested to be one of the sources of Aβ derived ROS (neuritic plaques are enriched in microglia). It is also important to note Aβ interacting with iron and copper could generate ROS. Indeed, a new analytical technique recently revealed that there is an increased tissue concentration of iron, copper and zinc around Aβ plaques (Rajendran et al., 2009) and this suggests that metal chelators have the potential role to reduce oxidative stress during AD (Ellis et al., 2010).

A recent study suggest the requirement of Met35 residue of Aβ peptide in ROS generation (Butterfield et al., 2010b). The fact that Aβ has been shown to be localized in mitochondrial membranes explains why AD patients suffer from the large degree of lipid peroxidation and mitochondrial dysfunction (Hansson Petersen et al., 2008; Oppermann et al., 1999). Disintegration of mitochondrial membranes and altered permeability impairs membrane potential and can readily cause leakage of cytochrome c and lead to apoptosis (Kagan et al., 2009). HNE reactivity not only results in disintegration of membranes but also modifies the structure and hence lowers the activity of some key housekeeping enzymes. Neprilysin, which is involved in the degradation of Aβ, is one of the targets of HNE and the modification that results in impaired activity and an increased accumulation of Aβ (Wang et al., 2009). A recent paper revealed that proteasome complex is also involved in the degradation of Aβ (Zhao and Yang, 2010). However, HNE can interact and deactivate proteasome resulting in accumulation of oxidized and altered proteins, which leads to impaired function (Farout et al., 2006). Therefore, lipid peroxidation-mediated chain reactions, especially HNE reactivity, could impair housekeeping enzyme structure and cause excessive increases in impaired proteins (Farout et al., 2006).

Increased levels of thiobarbituric acid-reactive substances (TBARS) and malondialdehyde, isoprostane levels have been reported in different regions of the brain, spinal cord, and body fluids of patients with AD (Butterfield et al., 2010a; Galbusera et al., 2004; Singh et al., 2010). It is well known that AD is associated with elevated levels of lipid peroxidation. Moreover it appears that patients with Parkinson diseases (PD) also suffer from the consequences of lipid peroxidation, since ROS are produced to a higher extent in the substantia nigra during PD (Ben-Shachar et al., 1992; Jenner, 1991; Navarro and Boveris, 2009; Zarkovic, 2003). The fact that antioxidant treatments significantly reduce the infarct size and attenuate the damage,

including lipid peroxidation in stroke, strongly suggests that ROS are heavily involved in the pathology of stroke (Deguchi et al., 2008; Lapchak et al., 2007; Loh et al., 2010). Indeed, lipid peroxidation is a damaging process that has been shown in a variety of neurodegenerative diseases, including AD, and other types of dementia, PD, stroke, Huntington disease, Niemann–Pick diseases, etc. (Adibhatla and Hatcher, 2008a).

Our current understanding of the repair of lipid peroxidation is far less developed than that of oxidative protein damage or DNA damage. Ca(2+)-independent phospholipase A(2) (iPLA(2)beta) appears to be one enzyme which could repair oxidized cardiolipin which is a component of the mitochondrial membrane (Kinsey et al., 2008; Zhao et al., 2010b). However, most of the enzymes in the family of phospholipase A2 are rather generators of oxidative stress and lipid peroxidation during prostaglandin synthesis from ArAc, a products of PLA2 reaction than repair of lipid peroxidation (Adibhatla and Hatcher, 2008b). Thus, inhibitors of secretory phospholipase A2 emerged as a potential tool to decrease inflammation and associated lipid peroxidation in addition to well-known inhibitors of cyclooxygenase 2 (COX2) (Hoda et al., 2009).

It is also important to note that phospholipase A2 generated lipid peroxidation is an enzymatic reaction. Thus this type of lipid peroxidation is designed by nature and could have physiological meaning (Nigam and Schewe, 2000). The physiological role of lipid peroxidation is enigmatic, but it could affect cell signaling such as proteasome-mediated degradation- associated signaling (Rapoport and Schewe, 1986) and could be important in the physiological remodeling of cellular membranes. The levels of lipid peroxidation in various organs, including brain (Martin et al., 1998; Michel et al., 2010), increase with aging. However, not all the lipid peroxidation products present to the same degree or at the same time with aging. Lipid antioxidants, especially lipid soluble vitamins and glutathione, glutathione-S-transferases and β-alanyl-L-histidine, which can quench lipid oxidants including HNE, are a naturally occurring phenomenon. Albumin and apolipoproteins and maybe some others with high intracellular concentration can bind and buffer HNE, resulting in detoxification of cellular milieu.

Taken together, brain contains a great deal of lipid material that is vulnerable to lipid peroxidation. The chain reaction which occurs can disintegrate membranes, impair cellular function of a wide range of proteins involved in signaling, metabolism and housekeeping enzymes. The repair process of lipid peroxidation is very limited, and moderate levels of lipid peroxidation could have significant physiological meaning for cell signaling and membrane remodeling. It is clear that lipid peroxidation is involved and associated with a variety of neurodegenerative diseases and aging. Thus, balance between these opposing roles may be important for homeostasis.

3. Oxidative protein damage, degradation and repair

ROS induced post translation modification of proteins is a magnitude higher than that of lipids and DNA (Nakamoto et al., 2007). The fragmentation of proteins due to the oxidation of the protein backbone is initiated by hydroxyl radical-mediated abstraction of the α-hydrogen atom from the amino acid residues forming a carbon centered radical (Berlett and Stadtman, 1997). This radical further reacts with O_2 and alkylperoxyl radical is formed, which, via intermediates (alkylperoxide, alkoxyl radical) finally give rise to hydroxyl protein derivative (Berlett and Stadtman, 1997) (Fig. 2).

All amino acid residues can be modified by the attack of ROS generating oxidation of amino acid side chains, protein–protein cross-linkages. Methionine and cysteine residues are even more prone to oxidation than others due to the presence of sulfur. Cysteine residues are converted to disulfide by oxidation and reduced back to cysteine under mild conditions such as in the presence of reducing agents like NADH without enzyme reaction. Methionine residues are transformed to methionine sulfoxide, which in turn modification can be repaired by methionine sulfoxide reductases, which catalyze the reduction of methionine sulfoxide back to methionine residues (Lim et al., 2011). The fact that the oxidation of methionine residues is reversible, points out that the modification of methionine residue could play a role in cellular regulation. Aging results in accumulation of the ROS-induced damage in methionine resides, which could be due to age-associated decreases in the activity of methionine sulfoxide reductases (Stadtman et al., 2005). The manipulation (depression or overexpression) of the methionine sulfoxide reductases could significantly affect the sensitivity to oxidative stress (Salmon et al., 2009; Zhao et al., 2010a), emphasizing the important role of housekeeping enzymes in the aging process.

Tyrosine is an important α-amino acid in the brain since it is precursors of neurotransmitters including dopamine, epinephrine and norepinephrine, readily nitrated and nitrotyrosine is often used as a marker of nitrosative stress (Souza et al., 2008). Tryptophan, which is an aromatic amino acid, is readily modified by ROS. Direct oxidation of lysine, arginine, proline and threonine residues give rise to carbonyl derivatives, which, due to the easy detection of and the strong association with aging, oxidative challenge is most often used as a marker of oxidative stress on proteins (Levine and Stadtman, 2001). It is important to note that carbonyl derivatives can be formed by the protein reaction with aldehydes from lipid peroxides or by glycation with glucose.

Elevated levels of protein carbonyls are linked to a variety of age-associated diseases and often correlate with the progress of disorders and diseases (Stadtman, 2001). Carbonylation and other ROS-associated post translation modifications of proteins readily inactivate proteins, and inactivated enzymes cannot catalyze biochemical processes. The accumulation of this oxidative "junk" can jeopardize cellular functions and fate (Stadtman, 2006). However, oxidative damage of proteins renders them susceptible to degradation by increasing the hydrophobicity of the surface of proteins (Chao et al., 1997), which could serve as a tag for the proteasome system, that leads to degradation (Shringarpure et al., 2003). This process does not consume ATP and is executed without ubiquitination and, interestingly, tau proteins, another hallmark of AD, are also degraded in this way (Grune et al., 2010). The age-associated accumulation of oxidized proteins could be a result of the impaired

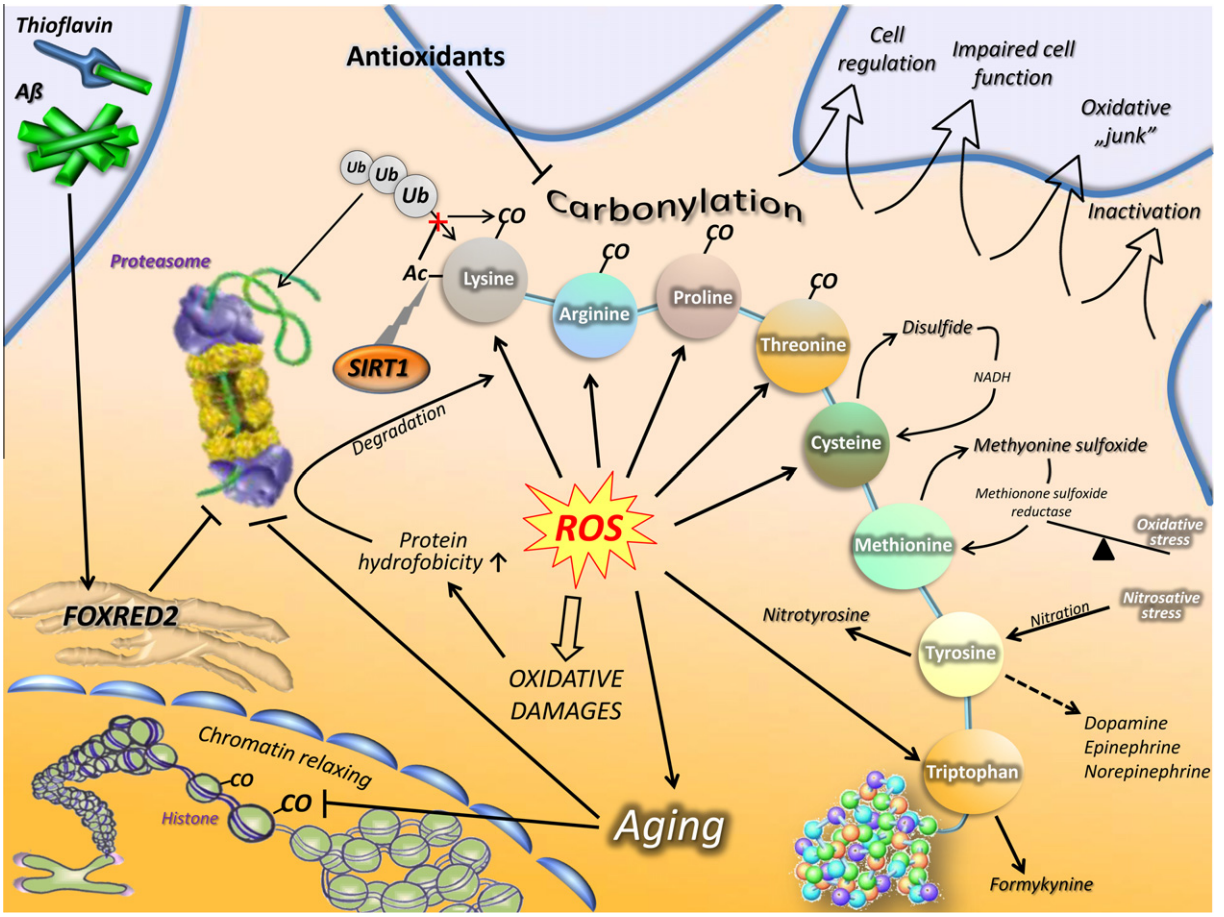

Fig. 2. Involvement of ROS in proteins in pathophysiology of cells. Proteins are major targets of ROS, amino acid residues such as Cys, Met, Arg, and Tyr being either reversibly or irreversibly modified. While some of reversible modifications are physiological regulators, irreversible modifications such as carbonylation are mostly harmful to cells but apparently not always. Irreversibly modified proteins are degraded by proteolytic enzymes such as proteasomes and Lon to reduce detrimental consequenses.

activity of the proteasome system. It has been suggested that during aging, as a result of a decreased rate of protein turnover, the life span of proteins increases creating a lengthened time for ROS-mediated protein damage (Nakamura et al., 2010; Terman et al., 2010). This finding could explain the reduced sensitivity and activity of the enzymes in aged organs as well as the impaired function. Indeed, it has been shown that antioxidant treatment of aged gerbils resulted in improved results in maze tests, increased the activity of glutamine synthase and proteases, and decreased levels of carbonyls (Carney et al., 1991). Although age-related the accumulation of carbonyl groups in amino acid residues is a well known phenomenon it is interesting to note that this is not always the case. Indeed, aging decreases the accumulation of carbonyl groups in histone, and thereby increases the charge of basic amino acid residues, resulting in more compact chromatin structure that would make transcription and repair of DNA less active. This is what exactly happening in aging (Sharma et al., 2006). Therefore, it cannot be ruled out that controlled oxidative protein modifications play significant physiological roles. In fact, dietary restriction that retards aging can increase histone carbonylation while the same regimen reduces carbonylation of other proteins in general.

A large accumulation of oxidative modifications on amino acid residues readily impairs cellular function (Radak et al., 2001a,b). The decreased activity of protein degrading systems with aging has also been observed and could significantly contribute to the accumulation of oxidized proteins and cellular junk (Mao et al., 2010). Indeed, it seems that the activity of proteasome is different in various cell types in the brain, E.G. lower in neurons than in glia and also lower in the nucleus than the cytoplasm. This finding could account for the differences in the accumulation of misfolded proteins in different cell types and organelles (Tydlacka et al., 2008). Impaired degradation of Aβ and tau is one of the reasons for enhanced accumulation of these proteins in the brain of patients with AD. The toxicity of Aβ involves upregulation of FOXRED2, which is an endoplasmic reticulum associated protein and a potent inhibitor of proteasome complex (Shim et al., 2011). Therefore, treatments that aim to increase the activity of Aβ and tau protein degrading enzymes, such as proteasome, insulin degrading enzyme or neprilysin is one of the most promising approaches to decrease the accumulation and toxicity of Aβ (Crowe et al.,

2009; Dahlmann, 2007; Himeno et al., 2011; Pritchard et al., 2011). The finding of a recent study nicely emphasizes the importance of protein homeostasis, and degradation. Supplementation of Aβ binding thioflavin, which interacts with Aβ to prevent aggregation, increased the life-span of *Caenorhabditis elegans* probably utilizing the beneficial effects on chaperons, autophagy, and proteasome (Alavez et al., 2011).

It cannot be ruled out that decreased deacetylating activity of sirtuins, especially SIRT1 during aging, could affect the rate of protein turnover. Acetylation of lysine residues could prevent the ubiquitination on the same residue and the degradation by proteasome. With aging, there is a significant increase in lysine acetylation in cerebellum and hippocampus associated with increased carbonylation (Koltai et al., in press; Sarga et al., unpublished). The acetylation related lack of ubiquitination could increase the life-span of proteins, resulting in increased carbonylation. Therefore, methods which could decrease acetylation, such as caloric restriction and physical exercise via the activation of SIRT1, might increase the rate of degradation. Indeed, methods which aim to prevent the age-associated decrease in proteasome activity and maintain the level of protein degradation appear to be useful in retarding aging and onset of neurodegenerative diseases (Crowe et al., 2009; Dahlmann, 2007).

The proteasome system is important, not just for studying the degradation of damaged proteins, as data indicate that it can also influence memory and remodeling after traumatic brain injury (Fischer et al., 2009; Kuczera et al., 2011; Szabo et al., 2010). The anaphase-promoting complex/cyclosome (APC/C) is an E3 ubiquitin ligase that targets proteins for proteasomal degradation and lack of APC/C results is impaired memory (Kuczera et al., 2011). Therefore, it appears that the proteasome system plays a complex role in the central nervous system. Mitochondrial protein quality control is mediated by Lon protease (Terman et al., 2010), which acts to prevent mitochondrial dysfunction during ischemia- induced oxidative stress in brain (Hori et al., 2002). The activity of Lon protease significantly decreases as a function of age, suggesting a critical role of Lon protease in the age-associated decrease in mitochondrial function (Ngo and Davies, 2007, 2009).

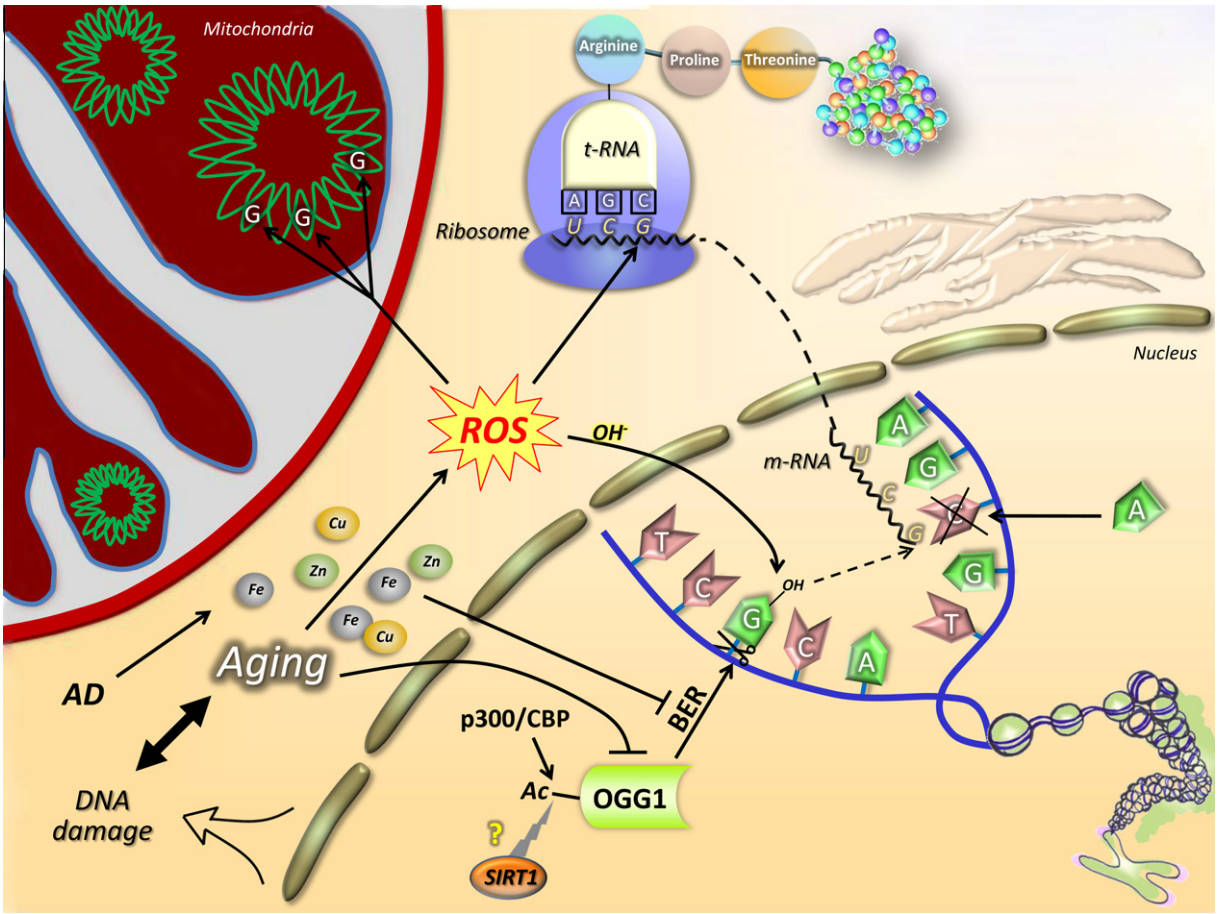

Fig. 3. Involvement of ROS in DNA in pathophysiology of cells. One of the most frequent oxidative modifications of DNA occurs on guanine base. Mitochondrial DNA is much more susceptible to ROS than nuclear DNA, leading to age-related dysfunction of the organelle. OGG1 is a rate limiting enzyme to repair the damage. The activity of the enzyme is apparently modulated by p300/CLB catalyzed acetylation and deacetylation by SIRT1. The fact that guanine can easily be oxidized may have physiological implications.

Oxidation of amino acid residues of proteins by ROS is an inevitable process, which could have a regulatory role in protein homeostasis that could explain the relatively large degree of ROS-associated conformational changes. However, enhanced accumulation of oxidized proteins could readily inhibit important cellular processes, and result in toxicity and cell death. The retardation of the impairment of the degrading systems as a result of aging and neurodegenerative diseases could be an important tool to decrease the rate of aging and modulate the consequences of neurodegenerative diseases.

4. DNA damage and repair in the brain during aging: neurodegenerative diseases

Age-associated increases in levels of ROS, especially during the last quarter of life, result in excessive oxidative damage to macromolecules, including DNA (Kaneko et al., 1997). Guanine is prone to oxidation due to its low reduction potential among DNA bases. It is modified primarily by the hydroxyl radical at or near diffusion-controlled rates (reviewed by (Dizdaroglu et al., 2002, 2008; Kanvah et al., 2010; Radak and Boldogh, 2010; Sies and Menck, 1992; von Sonntag, 1987; Wallace, 2002). More than 20 oxidation products of guanine base have been identified (Cooke et al., 2003) and among them the most abundant and well studied is 8-oxo-7,8-dihydroguanine (8-oxoG) (Boiteux et al., 2002; Nishimura, 2002). This review focuses on the physiology and pathology of 8-oxoG as well as on its repair. 8-oxoG levels in DNA increase with ischemia/reperfusion, acute exercise, neurodegenerative diseases and aging (Kaneko et al., 1996; Radak and Boldogh, 2010). When 8-oxoG is not repaired it is mutagenic, as it has been shown to pair with adenine (A) instead of cytosine (C) inducing G:C → T:A transversions (Nishimura, 2002). 8-oxoG is excised from DNA by formamidopyrimidine-DNA glycosylase (Fpg) in *Escherichia coli* and by its functional homolog 8-oxoguanine DNA glycosylase (OGG1) in mammals during base excision repair (BER) (Hazra et al., 2001; Nakabeppu et al., 2004; Nishimura, 2001). Guanine-rich DNA regions and susceptibility of guanine to ROS as the result of the low oxidation potential of guanine, reflect a natural strategy of the organism to adapt and evolve and utilize or abuse 8-oxoG. A wide range of observations also raise the possibility that oxidation of guanine in DNA and RNA might be described by a bell-shape dose–response curve (Radak and Boldogh, 2010), suggesting that a certain level of guanine oxidation might be necessary for normal physiological functions. The base level of 8-oxoG is estimated to be 1–2 per 10^6 guanine residues in nuclear DNA and about 1–3 per 10^5 in mitochondrial DNA, suggesting that up to 100,000 8-oxoG lesions could be generated in DNA per cell daily (Lindahl, 1993; Nakamoto et al., 2007). We have recently evaluated the complex physiological and pathophysiological roles of 8-oxoG, pointing out that a so called base level of 8-oxoG might be important for signaling and transcription (Radak and Boldogh, 2010) (Fig. 3).

Impaired function and accumulation of DNA damage in neurons have been suggested to be major factors related to brain aging and neurodegenerative diseases (Bohr et al., 1998; Schmitz et al., 1999). Indeed, using a rodent model, there are number of investigation which show that aging results in significant elevations in DNA damage (Caro et al., 2009; Ochoa et al., 2011; Swain and Subba Rao, 2011). Similar observation has been made from post mortem human brain samples.

Mecocci and co-workers have reported that aging results in significant increases in nuclear and mitochondrial 8-oxoG levels in human cerebral cortex and cerebellum (Mecocci et al., 1993). They have also shown that the increase is more significant in the brain of patients with AD (Mecocci et al., 1994). Neurons are specifically sensitive to accumulating 8-oxoG (Wang and Michaelis, 2010) and it appears that the capacity to repair 8-oxoG is dependent on brain regions (Cardozo-Pelaez et al., 2002), suggesting a link between the incidence of those neurodegenerative diseases where initiation occurs in a brain region specific manner. Age-associated decreases in the DNA repair activity of synaptosomes is associated with reduction in the levels of DNA repair enzymes and reduced mitochondrial axonal transport (Gredilla et al., 2010). Since upregulation of DNA repair suppresses DNA damage (Cardozo-Pelaez et al., 2002) methods that can elevate the activity of OGG1 could potentially decrease the pathology of certain diseases. It has been shown that during ischemic conditions OGG1 plays an important role in reducing 8-oxoG levels in nuclear DNA (Liu et al., 2011). Mitochondrial DNA is more exposed to ROS and the age-associated increase in 8-oxoG level is a magnitude higher in mtDNA compared to nDNA (Nakamoto et al., 2007). The failure of mtDNA repair is associated with chronic recurrent seizures in rat brain (Lin et al., 2010) suggesting that the consequences of seizures could impair mitochondrial function. Moreover, it was found that the failure of mitochondrial DNA repair accelerates the aging process and causes impaired behavior and neurodegeneration (Lauritzen et al., 2010). Mutation of parkin gene significantly increases the incidence of Parkinson Diseases (PD), which could be, at least partly, due to the fact that the parkin mediated protection of mtDNA is impaired by mutation, thus leading to reduced mtDNA repair capacity of PD patients (Rothfuss et al., 2009).

Brain is rich in metals and the concentration of metals is increases with aging (Mates et al., 2010). Li et al. (2009) noted the relationship with metal levels and base excision repair. AD is associated with the accumulation of metals and decreased levels of DNA repair (Coppede and Migliore, 2010; Obulesu and Rao, 2010). It has to be mentioned that OGG1 could induce cytokine production which might be involved in the chronic inflammatory process observed during AD (Wu et al., 2009). Therefore, the role of OGG1 in aging and age-associated neurodegenerative diseases appears to be very delicate (Radak and Boldogh, 2010).

It is known, that the activity of certain DNA repair proteins, including OGG1 can be modified by acetylation. Therefore, the effects of aging and neurodegenerative diseases on the protein acetyl transferases and/or protein deacetylases could be important. Acetylation of OGG1 is mediated by p300/CBP (Bhakat et al., 2006; Radak et al., 2011), while the deacetylating agents are not known. Preliminary data suggest that SIRT1 silencing increases the acetylation of OGG1 (Sarga et al., unpublished observation) suggesting that SIRT1 I could be actively involved in DNA repair. Aging increases the content of OGG1 in

the hippocampus of rats, but the acetylation of OGG1 is drastically decreased with aging, which could be the reason for the age-associated increase in 8-oxoG level in old rats (Koltai et al., in press).

ROS mediated damage to nDNA and mtDNA accumulates with aging and could contribute to the progress of aging and neurodegenerative diseases. Therefore, induction of DNA repair might be a potential tool to decelerate the aging process and improve the conditions of those who are suffering from neurodegenerative diseases. Number of DNA repair enzymes, including OGG1 is activated by acetylation and it appears that sirtuins are potent modulators of DNA repair.

5. Conclusion

ROS mediated oxidative damage to lipids, proteins and DNA is heavily involved in the progress of aging and neurodegenerative diseases. However, it appears that a certain level of lipid peroxidation, ROS-mediated post translational modifications of proteins, and even DNA damage, could be necessary for cells to function normally, including physiological signaling. Massive increases in oxidative damage jeopardize cell fate and function. Up-regulation of housekeeping enzymes, which are involved in the limited repair of lipids and proteins, are important means to decrease the rate of aging. Moreover, the increase in the activity of damaged proteins (or those which accumulation observed in neurodegenerative diseases) degrading systems is a therapeutic tool to fight against neurodegeneration. Oxidative DNA damage, especially the large accumulation of 8-oxoG is a hallmark of neurodegeneration and enhanced activity of repair enzymes, such as OGG1 could maintain normal cellular and organ functions, including cognitive and behavioral processes. Taken together, the avoidance of the accumulation of oxidative damage of lipids, proteins and DNA by the induction of repair processes is an important strategy to maintain healthy brain functions. Finally, it should be emphasized that repair processes can be induced by modest oxidative stress while extensive oxidative stress leads to harmful consequences in unprepared tissues, thus forming hormesis like effects of ROS.

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