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Nitrooxidative Stress and Neurodegeneration

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1. Introduction

Stress is the force on unit areas within a material that develops as a result of the externally applied force (Enciclopedia Britannica, 2011).

When I wrote the first paper on the stress syndrome in 1936, I tried to demonstrate that stress (…) is clearly a definable biological and medical phenomenon whose mechanisms can be objectively identified and with which we can cope much better once we know how to handle it (…) Stress is the nonspecific response of the body to any demand, whether is caused by, or results in, pleasant or unpleasant conditions (Selye, 1985).

Oxidative stress is defined as a persistent imbalance between antioxidants and pro-oxidants in favor of the latter, resulting in (often) irreversible cellular damages (Probiox, 2011).

Nitrosative Stress: A condition that occurs when the production of highly reactive nitrogen-containing chemicals, such as nitrous oxide, exceed the ability of the (...) body to neutralize and eliminate them. Nitrosative stress can lead to reactions that alter protein structure thus interfering with normal body functions (Oxford Dictionary of Sports Science & Medicine, 2007).

The four quotations collected above illustrate confusion with the notion of stress. In physics, in Hooke's law, 'stress' means a force acting on an elastic material and producing a proportional amount of deformation, or strain. However, according to Selye, who introduced the notion of 'stress' into (bio)medicine, it is not a kind of force acting on an organism (such force is called 'stressor'), but a response of an organism to such a force. In fact, Selye's definition of 'stress' is more similar to the notion of 'strain' in Hooke's law. Contemporary uses of the term 'stress' in biomedical scientific literature are very diverse; the last two examples define stress as an imbalance which occurs inside a body and leads to its damage. These definitions are very different from Selye's definition of stress.

Several distinguished authors wrote reviews about oxidative and nitrosative stress, but many either did not define these terms at all, or defined them vaguely and indirectly. For example, in a recent review one of the most prominent biochemists working in the field of redox and free radicals biochemistry professor Barry Halliwell only listed reasons why tissue injury causes oxidative stress and what oxidative stress means in the context of human disease (Halliwell, 2009); it seems that he implicitly defined oxidative stress as a result of tissue injury (or, perhaps, response to it) rather than its cause. However most

authors, indeed, use terms ‘oxidative stress’ and ‘nitrosative stress’ to describe situations of persistent imbalance between production and removal of oxidising free radicals leading to their increased level and resulting in harmful effects on biological molecules, cells and tissues. For example professor Helmut Sies defined ’oxidative stress’ as a condition occurring when the generation of reactive oxygen species (ROS) in a system exceeds the system's ability to neutralize and eliminate them. This imbalance can result from a lack of antioxidant capacity caused by disturbance in production, distribution, or by an overabundance of ROS from endogenous sources or environmental stressors (Brenneisen et al., 2005; Sies, 1997). Shouldn't we conclude that oxidative stress is always linked to the damage of biological macromolecules and the disruption of cellular homeostasis? However, the title of the other paper from Sies's laboratory includes the phrase "Peroxynitrite signalling: (...) activation of stress-responsive pathways" (Klotz et al., 2002), which is suggestive of that cells not only receive harm from nitrooxidative stress but also can respond to in an orderly manner, which depends on circumstances and may be either positive or detrimental.

Concise and amazingly fitting definition of the term ‘stress’ we found in the English-Polish dictionary (Stanislawski, 1999). This definition, translated back to English, reads the following: ‘stress is the pressure of circumstances’. In the case of oxidative and nitrosative stress the said circumstances are disturbances in the balance between production and removal of reactive forms of oxygen and nitrogen, most of which are free radicals. The amount of literature on this subject is so large, that its comprehensive review would require a multi-thousand-page book. In the present chapter we will concentrate on the following specific subjects: (1) why nitrooxidative stress is considered harmful, (2) cellular metabolism of reactive oxygen and nitrogen species, and (3) how nitrooxidative stress can contribute to some major neurodegenerative diseases.

2. Free radicals

The recent version of the International Union of Pure and Applied Chemistry (IUPAC) *Recommendations on Nomenclature of Inorganic Chemistry* (IUPAC, 2005), known as *the Red Book*, defines a **radical** as an atom or molecule with one or more unpaired electrons. An unpaired electron may be indicated in a formula by a superscript dot. A radical may have positive, negative or zero charge. Metals and their ions or complexes often possess unpaired electrons but, by convention, they are not considered to be radicals. The terms ‘radical’ and ‘free radical’ are frequently used interchangeably, although more correctly radicals may be called ‘free’ only when they can freely diffuse in their environment.

The aforementioned definition is also strictly applicable to organic radicals, i.e. radicals containing carbon. However, we shall bear in mind that not long time ago such a view was difficult to accept. This was because, after many futile attempts to isolate carbon-containing radicals, XIX-century chemists concluded that carbon must always be tetravalent (i.e. form four bonds) and organic radicals cannot exist. Although the first organic free radical, the trityl (triphenylmethyl) radical (fig. 1), was discovered by Gomberg in 1900, for many years this discovery was viewed only as a curiosity (Henderson, 2000). Besides, trityl radical does not contain oxygen.

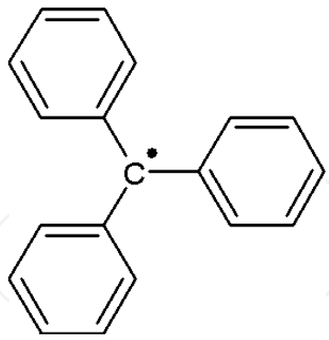


Fig. 1. Trityl (triphenylmethyl) radical.

The concept of oxygen free radicals toxicity as the major contributor to various pathologies has been developed in the middle of XX century, at the intersection of studies on mechanisms of oxygen toxicity and on toxic effects of ionizing radiation. On one hand, it was already very well known that eukaryotic organisms cannot survive without oxygen, yet at the same time oxygen is toxic. This Janus-faced property of oxygen is sometimes called the 'paradox of aerobic life', or the 'oxygen paradox' (Fridovich, 1975). Toxic effects of exposure to oxygen at increased partial pressure, particularly evident in human central nervous system and lungs, have been described in the late XIX century, but after more than 50 years their mechanism remained unknown (Donald, 1947). On the other hand, harmful effects on living organisms of ionizing radiation, which become known shortly after its discovery (Inkret et al., 1995), were already explained, mostly by the intracellular radiolysis of water molecules into H^+ and OH^- radicals. These radicals either by itself cause oxidative damage to the cells, or further recombine to nascent toxic radicals such as superoxide.

In 1954 the presence of free radicals in biological materials not subjected to ionizing radiation was discovered (Commoner et al., 1954). Almost at the same time Gershman, Gilbert and collaborators put forward a hypothesis that the majority of harmful effects of both oxygen and ionizing radiation could be attributed to the same mechanism, namely the formation of oxygen radicals (Gerschman et al., 1954). This hypothesis was later developed into the theory that oxygen radicals are continuously generated in all living cells, starting point of their cellular metabolism being the formation of superoxide radical anion (Fridovich, 1983). Halliwell and Gutteridge (1984) called this concept 'the superoxide theory of oxygen toxicity'. Currently it is generally accepted that oxygen free radicals are ubiquitous in the living matter; they are continuously produced by a variety of reactions (enzymatic and nonenzymatic), and at the same time continuously removed by the other variety of reactions. Indeed, the generation of oxygen radicals in living cells is not a pathology, but the fundamental physiological phenomenon.

Moreover, molecular oxygen (O_2) by itself is a double radical (a biradical), having two unpaired electrons with parallel spin states. This arangement is quite fortunate, as it makes O_2 a stable radical and prevents spontaneous ignition of carbon-based materials in the oxygen atmosphere. On the other hand, as a consequence, oxidation by molecular

oxygen can easily occur only by the transfer of single electrons. However, organic molecules which are substrates for biological oxidations do not contain unpaired electrons. Therefore molecular oxygen could accept a pair of electrons from an organic substrate only when one of the electrons of oxygen or one of the electrons from the donating substrate inverts its spin. This can happen, but would require a substantial activation energy.

The solution utilised by living cells to decrease activation energy for oxidations relies on conducting two oxidations stepwise, by a close sequence of two single-electron transfers (Miles, 2003). This arrangement works nicely, but its side effect is a relatively high probability that products of the first one-electron reduction of oxygen, i.e. oxygen radicals, will not engage in the second one-electron reduction step but enter the intracellular (or extracellular) milieu instead.

As mentioned already, oxygen free radicals have potential to react with (that is, to oxidize) practically any organic molecule they come in contact with. These reactions may inflict damage to cellular constituents including macromolecules (proteins, nucleic acids), aminoacids, sugars, lipids (polyunsaturated fatty acids in particular) etc. However, under normal metabolic conditions the actual concentration of free radicals in biological matter (i.e. living cells and extracellular material) is pretty small. Chance et al. (1979) estimated that in rat liver equilibrium concentration of superoxide anion radical is in the order of 10^{-12} to 10^{-11} M and that of hydrogen peroxide is only 3 orders of magnitude greater. Only if equilibrium is disturbed, which may be called nitrooxidative stress, oxygen free radicals and products of their metabolism which are strong oxidants, all called collectively reactive oxygen and nitrogen species (ROS and RNS), do have potential for inflicting damage to vital constituents of the living cells (McCord, 2000).

3. Cellular metabolism of reactive oxygen and nitrogen species

Reactions of ROS and RNS which occur in living cells are irreversible and may be presented as a cascade (fig. 2) that starts with generation of **superoxide radical** ($O_2^{\bullet -}$). This free radical appears mainly in mitochondria; some authors estimate that 2-4% of oxygen metabolized by mitochondrial respiratory chain leaves it as superoxide (Turrens, 2003). $O_2^{\bullet -}$ is also a product of certain enzymatic reactions localized outside mitochondria, in particular NADH oxidation conducted by non-mitochondrial NADH oxidases called NOX (Sorce & Krause, 2009). Some NOX isoenzymes are end parts of 'plasma respiratory chains' called also 'plasma membrane oxidoreductases' (PMOR) present in many cell types including neurons (Wright & Kuhn, 2002). ECTO-NOX present on cell surface are supposed to release $O_2^{\bullet -}$ into the extracellular milieu, while other isoforms of NOX produce superoxide radical intracellularly.

An additional source of superoxide radical is **singlet oxygen** ($^1O_2$), generated in photosensitization reaction which takes place *in vivo* upon exposure of cells to light, e.g. in the retina. Although not a free radical, $^1O_2$ is a highly reactive molecule, thus it belongs to ROS. Some authors claim that singlet oxygen by itself can damage membranes and other cell components (Winkler et al., 1999). Importantly, singlet oxygen cannot be removed enzymatically but only in reactions with non-enzymatic antioxidants. Singlet oxygen can be also reduced to $O_2^{\bullet -}$.

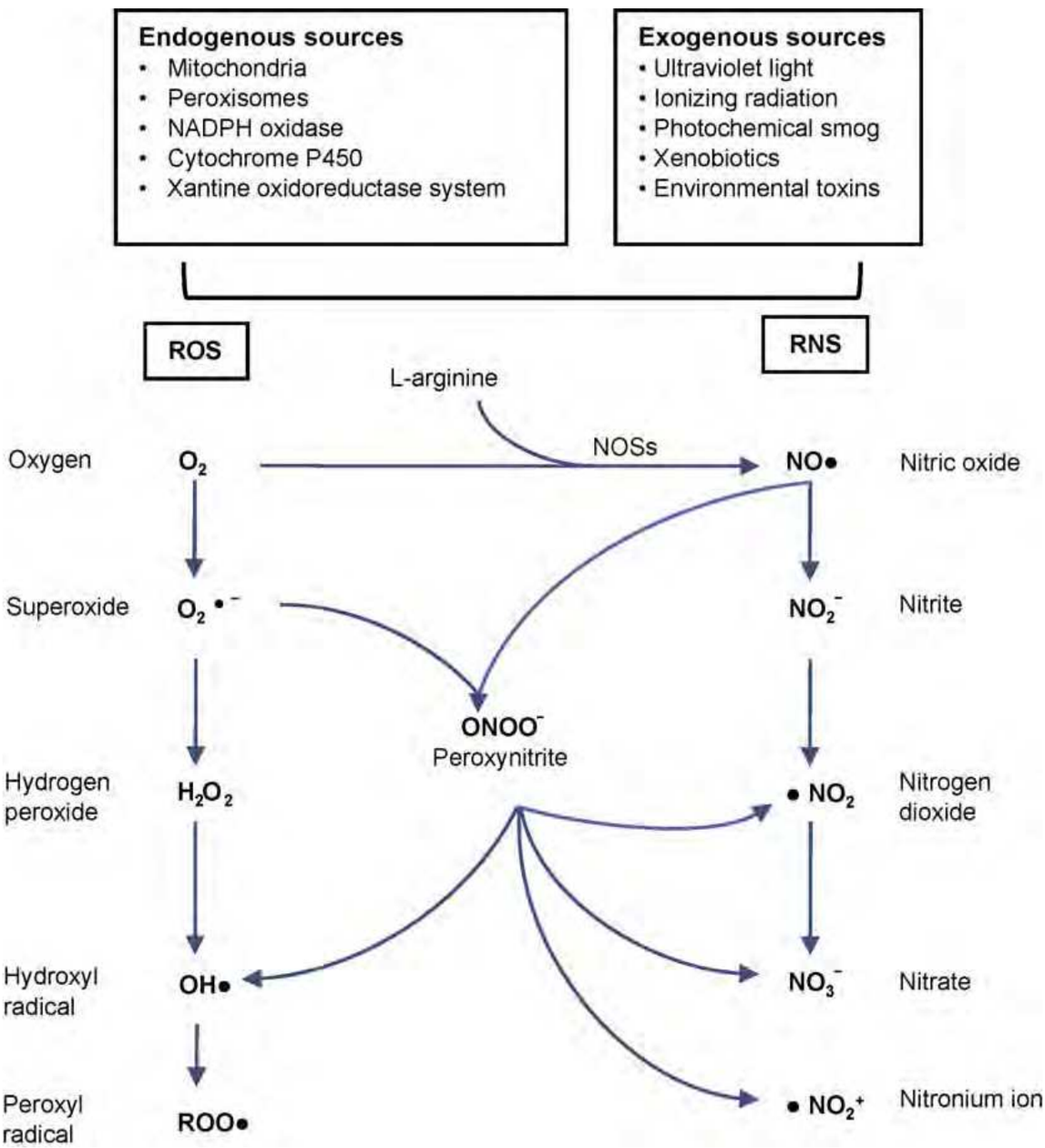


Fig. 2. Cascade of radical reactions in the cell and the most important reactive oxygen and nitrogen species. Main sources of ROS and RNS are listed in the upper part of the figure. Reproduced from Mangialasche et al. (2009). © Elsevier, with permission.

Cells can be damaged directly by superoxide radical (Benov, 2001), or by its metabolites, hydroxyl radical and peroxynitrites. Compared to other radicals superoxide is not very

reactive chemically; moreover it may react only either with itself (dismutation), with another radical such as nitric oxide, or with a a metal. Hovewer, although dismutation of $O_2^{\bullet-}$ occurs spontaneously, it is a second order reaction with respect to substrate concentration, ineffective in removing it at low concentrations. Since even in subnanomolar concentrations superoxide is toxic, in particular to some mitochondrial enzymes (e.g. aconitase), all cells are equipped with enzymes superoxide dismutases (SOD), which very efficiently convert superoxide to hydrogen peroxide (see below).

Of all ROS, **hydrogen peroxide** is a molecule with the longest half-life, and it may achieve the highest intracellular concentration. Moreover, it has the ability to diffuse across biological membranes. Hydrogen peroxide by itself is not particularly toxic or dangerous to the cells, but in reaction catalyzed by iron ions (Fe^{2+}) it is converted to hydroxyl radical ($OH^{\bullet}$) (Buonocore et al., 2010). This reaction, known as the Haber-Weiss reaction, generates hydroxyl radicals from H_2O_2 and superoxide. It can occur in cells, being responsible for oxidative stress. It is a two-step catalytic cycle. The first step involves reduction of ferric ion to ferrous:

$$Fe^{3+} + O_2^{\bullet-} \rightarrow Fe^{2+} + O_2$$

The second step, known as the Fenton reaction, regenerates ferric ion:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^{\bullet}$$

Hydroxyl radical is regarded the most cell-damaging oxidant (Cheng et al., 2002). Its half life is extremely short (10^{-6} s, 3 orders of magnitude shorter than $O_2^{\bullet-}$) and it acts locally, very close to site of its generation. It reacts mainly with alkyl groups or with polyunsaturated fatty acids, initiating chain peroxidation (see below).

Peroxynitrite ($ONOO^-$), the most important RNS, is a product of reaction of superoxide radical with nitric oxide. It is not a radical but is a potent oxidant and nitrating agent. It can nitrate tyrosine residues of proteins (generating nitrotyrosine) – this protein modification can affect enzyme activities and increase susceptibility of proteins to proteolysis (Abello et al., 2009). It also oxidizes fatty acids and induces DNA strand breaks (Ascenzi et al., 2010).

ROS and RNS react with many important biomolecules. **Lipid chain peroxidation** is particularly important since it affects functioning of biological membranes: their fluidity, permeability, ion transportation and inhibits metabolic processes. Peroxidation of mitochondrial membrane lipids (e.g. cardiolipin) may induce apoptosis (Kagan et al., 2009). Lipids containing polyunsaturated faty acids (PUFA) are particularly vulnerable to peroxidation. Lipid chain peroxidation consists of three phases: initiation, propagation and termination (fig. 3). Initiation phase includes hydrogen atom abstraction in reaction with diiferent radicals (e.g. $OH^{\bullet}$) and produces a lipid radical ($L^{\bullet}$). $L^{\bullet}$ reacts with oxygen to produce lipid peroxyl radical ($LOO^{\bullet}$) that can abstract hydrogen atoms from another lipids to produce lipid hydroxyperoxide (LOOH) and another radical (propagation). This reaction can repeated many times – one hydroxyl radical can damage thousands of PUFA chains. The 'chain peroxidation' terminates when two radicals react together forming non-radical species (Catala, 2010).

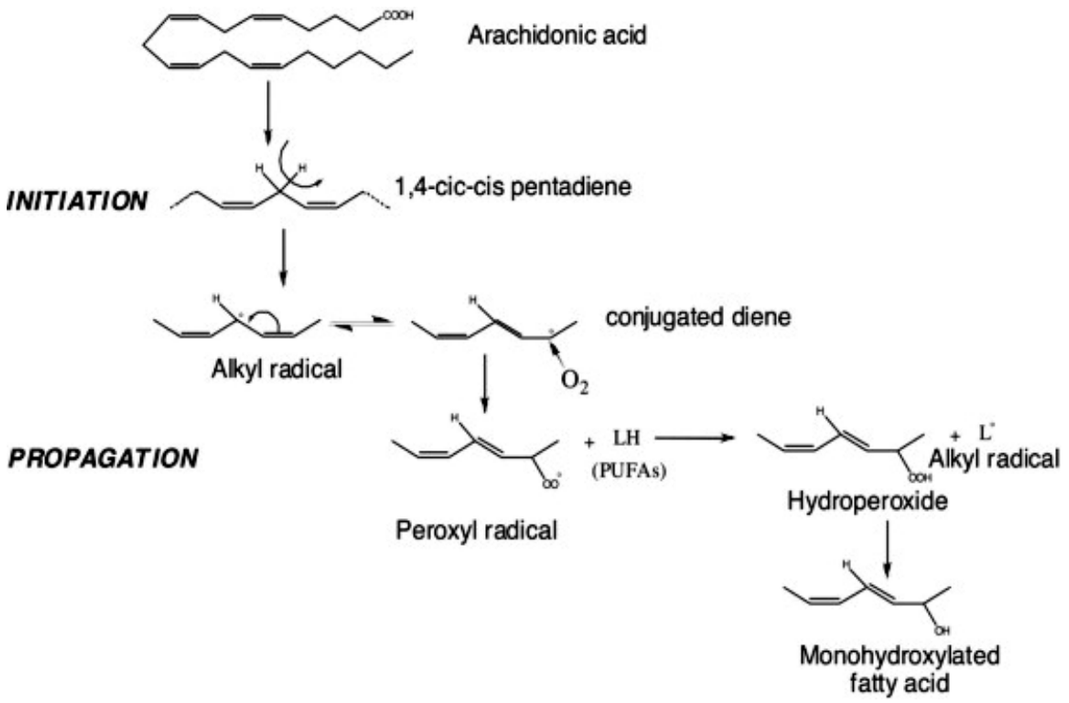


Fig. 3. Lipid peroxidation mechanism. Arachidonic acid was used as an example.
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Cells possess various mechanisms responsible for minimizing free radical hazard – 'low-weight' non-catalytic antioxidants and antioxidant enzymes. Superoxide dismutases can be regarded as 'first line of defense' against ROS. This group of enzymes catalyze reaction of superoxide radical dismutation (i.e. conversion of $O_2^{\bullet-}$ to H_2O_2). Although this reaction occurs spontaneously, lack of catalyst would increase $O_2^{\bullet-}$ concentration, potentiate chain lipid peroxidation and lead to more intensive generation of RNS. Mammals possess three isoforms of superoxide dismutases: 'cytoplasmic' (CuZn-SOD, SOD1), 'mitochondrial' (Mn-SOD, SOD2) and 'extracellular' (EC-SOD, SOD3). Most of cellular dismutase activity (50-80%) is attributed to SOD1 (Faraci & Didion, 2004) but it is SOD2 that is thought to be crucial for cell functioning. SOD2 gene knockout was lethal in mice (Huang et al., 2001) and decrease in SOD2 activity ($Sod2^{+/-}$) led to neuronal loss and cancer progression (Van Remmen et al., 2003).

It should be also stressed that recently ROS and RNS are regarded not only as toxic byproducts of metabolism but also as **important signaling molecules**. Two important and thoroughly examined ones are hydrogen peroxide and nitric oxide. Hydrogen peroxide has relatively long half-life and can penetrate biological membrane. Concentration of H_2O_2 in the cell is also relatively high. It is believed to be involved in various processes including immune cell activation, remodeling of vessels, cell growth and many others (see reviews by Veal et al. (2007) or by Giorgio et al. (2007)). Hydrogen peroxide level is precisely regulated

by growth factors. It inhibits phosphatases that are involved in propagation of signal induced by growth factors. It also induces tyrosine phosphorylation by activation of MAP kinases.

Observation that at least some of ROS and RNS are important signaling molecules and their levels are precisely regulated in the cell leads to the idea of 'redox homeostasis'. It is hypothesized that ROS/RNS are especially involved in regulation of proliferation and cell death of cells (Clement & Pervaiz, 1999). Reducing environment and low levels of ROS/RNS would suppress proliferation and is characteristic for 'resting' cells (see also fig. 7). Higher level of oxidants would promote proliferation and a bit higher apoptosis. However, above some range apoptosis would be suppressed due to oxidation of caspases (Hampton & Orrenius, 1998).

4. Nitrooxidative stress – Contribution to the pathomechanisms of neurodegenerative disorders

Neurodegenerative diseases – innate or acquired disorders of nervous system – can be defined by degeneration and death of neuronal cells. There is a regional or even cell-type-specific selectivity of neuronal failure and loss in different diseases. For example in Alzheimer's disease loss of cholinergic neurons occur mainly in the forebrain, in Parkinson's disease dopaminergic neurons in substiantia nigra are selectively injured and in glaucoma retinal ganglion cells are degenerating. Neuronal tissue seems to be vulnerable to damage caused by reactive forms of oxygen and nitrogen: oxygen metabolism is high and neurons contain high amounts of PUFA. Also oxidative/nitrosative damage to the neuronal tissue seems to be an early hallmark of degeneration in different pathologies. Thus, despite region-specific sensitivity, damage resulting from processes including ROS and RNS may be proposed as unifying mechanism for neurodegeneration (Ischiropoulos & Beckman, 2003). Common mechanisms involved in neurodegenerative disease leading to oxidative stress could include the inhibition of mitochondrial metabolism, neuronal excitotoxicity, and neuroinflammation (Golden & Patel, 2009). Examples further in this chapter show that nitrooxidative stress can be a key player in pathomechanisms of diverse neurodegenerative diseases.

4.1 Nitrooxidative stress and Alzheimer's disease

Alzheimer's disease (AD) is the most common type of dementia and in fact the most common neurodegenerative disorder. Most of the cases are sporadic but 5-10% of cases are familial and associated with mutations in genes of proteins involved in amyloid-β (Aβ) metabolism. The disease is characterized by progressive cognitive decline and neuropathological alterations: senile plaques built up by Aβ peptide and neurofibrillary tangles composed of hyperphosphorylated tau protein. Gross brain atrophy prominent in AD is caused by massive loss of neurons mostly in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Possibilities of therapeutic interventions are currently modest.

Numerous reports demonstrate both oxidative and nitrosative damage in the brains of AD patients (reviewed by Mangialasche et al. (2009)). This damage concerns lipids since

numerous markers of lipid peroxidation (*inter alia* malondialdehyde, acrolein, 4-hydroxy-2-nonenal and F2-isoprostanes) were found to be upregulated in brains of AD patients. Also markers of nucleic acid damage (like 8-hydroxydeoxyguanosine) or protein modification (like 3-nitrotyrosine (3-NT) or protein carbonyls) were upregulated.

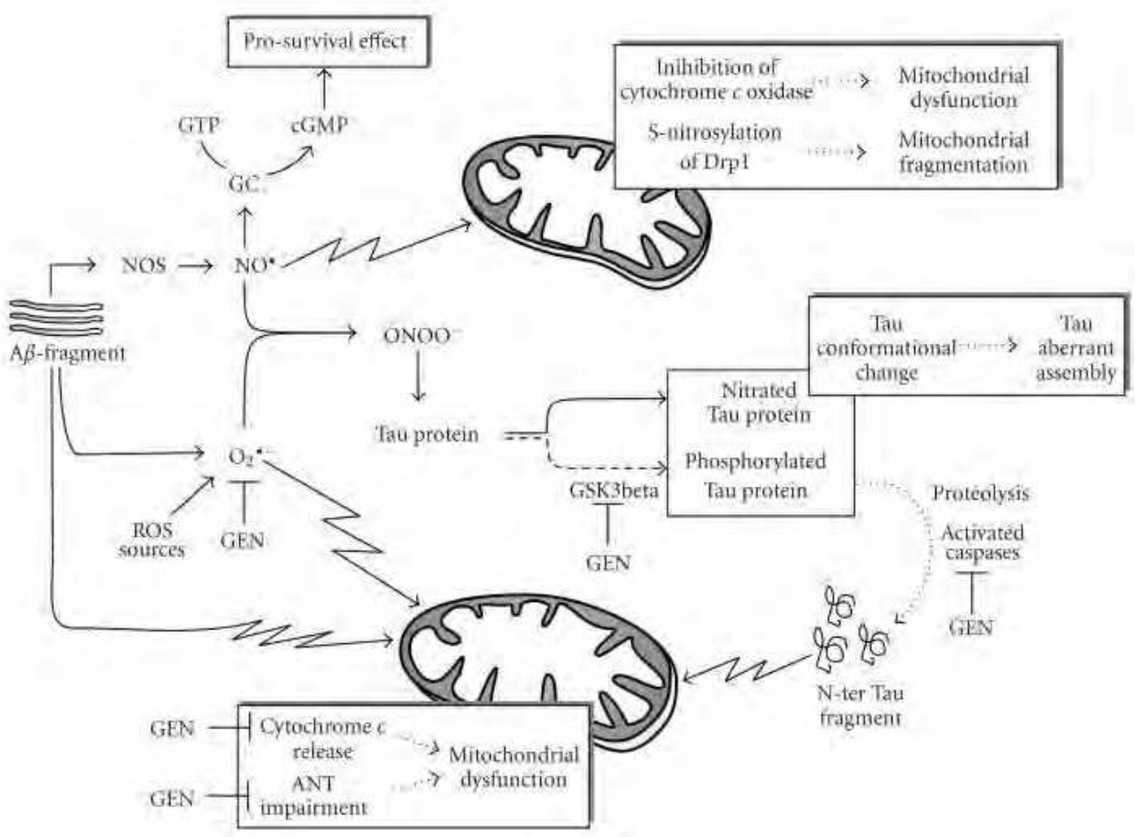


Fig. 4. Overview of the interplay between Aβ, Tau, oxidative/nitrosative stress, and mitochondria. Reproduced from Bobba et al. (2010). © Antonella Bobba et al., open access article.

Importantly, increased oxidative damage seems to be an early event in AD pathology since it is observed already in mildly cognitively impaired patients (Keller et al., 2005). This observations led to an idea of using various markers of oxidative/nitrosative damage as an early marker of AD pathology allowing to start therapeutical intervention in an early stage of the disease (see review by Galasko & Montine (2010)). Currently, F_2-isoprostane, a lipid peroxidation product, seems to be the most promising biomarker (de Leon et al., 2007; Pratico et al., 2002). Unfortunately while distinguishing AD and non-AD patients with markers measured in the cerebrospinal fluid seems to be pretty reliable there are some problems with applying these measures to plasma or urine samples.

Results obtained in different animal models of AD are consistent with those observed in patients. Oxidative lipid damage seem to be an early event in transgenic mouse models of AD amyloidosis and in fact precede Aβ plaque formation (Pratico et al., 2001).

One simple explanation of increased nitrooxidative stress in AD is Aβ toxicity. This is in concert with Aβ hypothesis that is currently the most popular one and assumes that formation of Aβ plaques is a central event in AD patophysiology. Aβ is thought to be capable of forming of free radicals by generation of hydrogen peroxide (Jomova et al., 2010). This potential of Aβ to generate free radicals was confirmed by *in vitro* studies (Ill-Raga et al., 2010) and is connected with its affinity to redox metals (eg. copper and iron). From the other side in experimental models nitrooxidative stress precedes Aβ plaques formation. There is also data showing that oxidative stress can actually alter metabolism of Aβ precursor protein and tau and thus promote formation of plaques and tangles (Li et al., 2004; Lovell et al., 2004; Ohyagi et al., 2000).

An apparent hallmark of AD is decreased brain energy metabolism. Even when corrected for decreased number of neurons brain glucose metabolism is markedly decreased in AD patients (Heiss et al., 1991; Ogawa et al., 1996). This altered energetics may be attributed to mitochondrial dysfunction and promote production of ROS and RNS. Recent reports showed that it could be Aβ that affects mitochondria and alters their functioning. Aβ can access the mitochondrial matrix and accumulate in the mitochondria affecting activity of mitochondrial enzymes and potentiate release of ROS (Chen & Yan, 2006).

Last but not least inflammatory processes seem to be a part of AD pathology - microglia are present in the Aβ plaques and in their surroundings (Rozemuller et al., 2005; Schwab & McGeer, 2008). Also Aβ can *in vitro* activate microglia (Jekabsone et al., 2006). Activation of microglia is associated with production of ROS and potentially leads to damage of neighbouring neurons (Block et al., 2007).

4.2 Nitrooxidative stress and Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease. Disease progression starts with motor deficiencies – rigidity, shaking, slowness of movement and as progresses difficulties with gait and walking arise. In the advanced stages of the disease symptoms also include cognitive decline and behavioural changes. Pathologic hallmarks of PD are degeneration and death of dopaminergic neurons in substantia nigra and presence of Lewy bodies – intracellular aggregates of protein α-synuclein. Treatment includes stimulation of dopamine signalling, e.g. by supplementation with dopamine precursor – L-DOPA or by administration of dopamine agonists (Lew, 2007).

Nitrooxidative stress is evident in the brains of PD patients. Increased levels of lipid peroxidation products: 4-hydroxy-2-nonenal and thiobarbituric acid reactive substances were found in substantia nigra of PD patients (Yoritaka et al., 1996). Also markers of oxidative damage to DNA and RNA like 8-hydroxyguanosine were found to be upregulated in this region (Zhang et al., 1999). Protein oxidation was found to be increased in PD, eg. levels of protein carbonyls were higher than in age-matched controls (Alam et al., 1997).

Also data obtained from animal models of PD imply increased nitrooxidative stress. PINK1 and DJ-1 null mice had increased levels of oxidative stress markers (Andres-Mateos et al., 2007; Gautier et al., 2008). Toxicity of overexpressed α-synuclein in mice is also thought to be associated with free radicals (Masliah et al., 2000).

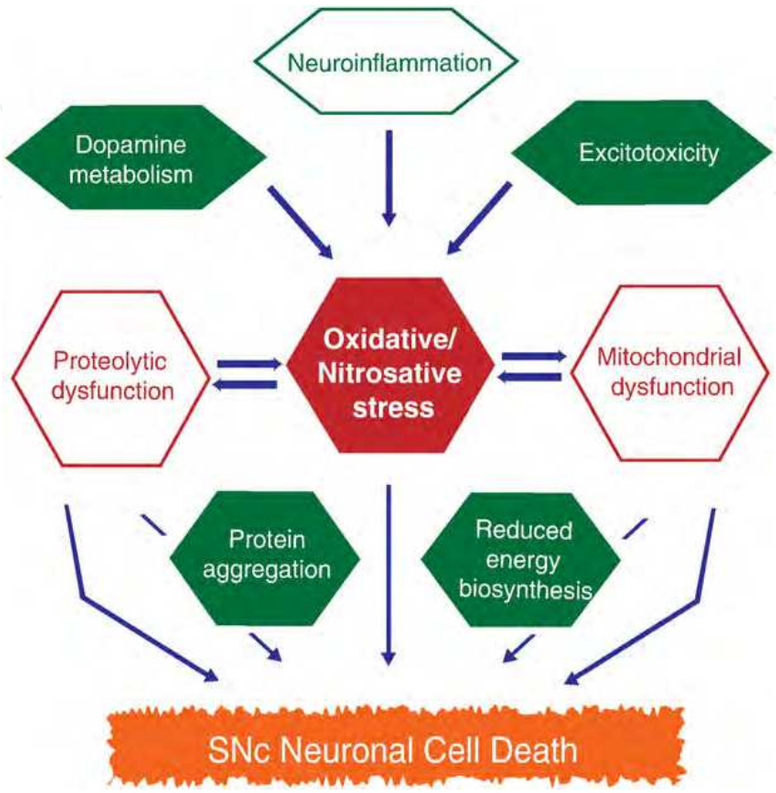


Fig. 5. Oxidative and nitrosative stress as a central event in PD pathology. SNc – substantia nigra compacta. Reproduced from Tsang & Chung (2009). © Elsevier, with permission.

This upregulation of oxidative/nitrosative stress might be related to mitochondrial dysregulation observed in PD patients (see fig. 5). There is direct evidence showing decreased activity of mitochondrial complex I isolated from substantia nigra and frontal cortex of PD patients (Parker, Jr. et al., 2008; Schapira et al., 1990). Also increased oxidation of this protein complex has been shown in PD patients (Keeney et al., 2006). It seems that abnormalities in functioning of complex I lead to increased generation of ROS. Importantly, administration of several complex I inhibitors lead to PD symptoms: motor deficiencies and death of dopaminergic neurons. Accidental exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, impurity in illegally synthesized recreational drug 1-methyl-4-phenyl-4-propionoxypiperidine, MPPP) that is precursor of neurotoxic 1-methyl-4-phenylpyridinium (MPP^+) leads to a rapid development of irreversible parkinsonian symptoms (Langston et al., 1983). Due to its selectivity, MPTP administration to laboratory animals is widely used as a model of PD. On the other hand ROS and RNS might be involved in decrease of complex I activity especially by involvement of $ONOO^-$ (Navarro & Boveris, 2009).

Overstimulation of N-methyl-D-aspartate receptor (i.e. excitotoxicity) can be also involved in PD pathology. Resulting Ca^{2+} influx leads to activation of NO synthase and overproduction of NO that can react with $O_2^{\bullet -}$ (overproduced due to mitochondrial dysregulation) and generate highly toxic $ONOO^-$. This mechanism seems to work in mice treated with MPTP since various NO synthase knockout mice were resistant to MPTP toxicity (Liberatore et al., 1999; Przedborski et al., 1996).

Activation of microglia is also present in PD pathology. Such activation was observed in PD patients *in vivo* by PET imaging (Gerhard et al., 2006). It was also noted in the brains of MPTP-intoxicated patients (Langston et al., 1999) and in animals that received MPTP in order to induce PD symptoms (Czlonkowska et al., 1996; Kohutnicka et al., 1998). One link between this persistent activation of microglia and pathology is increased production of ROS/RNS.

4.3 Nitrooxidative stress and glaucoma

Glaucoma – neurodegenerative disease of the retina – is the most common cause of irreversible blindness worldwide (Resnikoff et al., 2004). Progression of glaucoma is associated with gradual narrowing of visual field, typically starting from the periphery. It is sometimes called 'a sneaky theft of sight' since progression of the disease may remain unnoticed for many years. Pathological changes in glaucoma concern retinal ganglion cells and its axons that build optic nerve (Foster et al., 2002). Some recent data point that glaucoma is not limited to retina and optic nerve but also affect upstream components of the visual pathway (Gupta & Yucel, 2007). Current treatment strategies concentrate on lowering intraocular pressure (IOP), a condition observed in most but not all of the cases of glaucoma.

Measuring nitrooxidative damage biomarkers is a bit easier in case of glaucoma as aqueous humor and vitreous humor are pretty easily accessible. MDA level was two times higher in aqueous humor obtained from patients with open angle glaucoma than from healthy controls (Ghanem et al., 2010; Yildirim et al., 2005). Also open angle glaucoma patients had higher level of oxidative DNA damages in cells of trabecular meshwork (structure engaged in control of IOP). Importantly these alterations correlated well with IOP and narrowing of visual field (Izzotti et al., 2003; Sacca et al., 2005). Glutathione, ascorbic acid and tyrosine – low molecular antioxidants were downregulated in glaucoma patients (Ferreira et al., 2004), whereas SOD activity was diminished.

Also in animal models of glaucoma markers of oxidative/nitrosative stress were upregulated. MDA was upregulated in a model of high-pressure glaucoma (Moreno et al., 2004). Also carbonyl groups in retinas from these animals were upregulated. SOD activity in a model of high-pressure glaucoma was diminished (Moreno et al., 2004).

Signs of mitochondrial dysregulation were also noted in glaucoma patients. Abu-Amero et al. (2006) revealed association between primary open-angle glaucoma and changes in mitochondrial DNA. They also found that mitochndrial respiratory activity was significantly decreased in these patients. In normal tension glaucoma mutations in genes coding mitochondrial proteins were found (Mabuchi et al., 2007; Wolf et al., 2009).

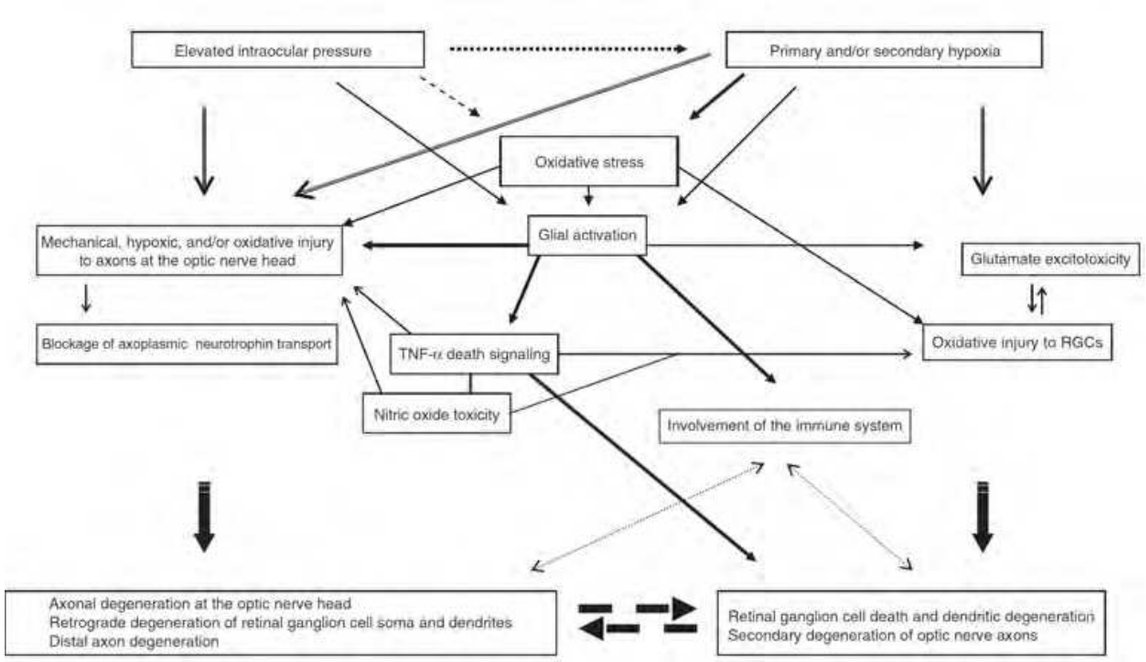


Fig. 6. Multiple proposed pathogenic mechanisms in glaucoma seem to related to oxidative stress as a common pathway. Reproduced from Tezel (2006). © Elsevier, with permission.

It is well known that glutamate administered into vitreous humor is toxic for retinal ganglion cells (Lucas & Newhouse, 1957; Quigley, 1999). Also N-methyl-D-aspartate intravitreous administration causes massive retinal ganglion cell loss (Nakazawa et al., 2005). The ability of glial cells to buffer extracellular glutamate might be impaired (Martin et al., 2002; Moreno et al., 2005). Although, some earlier reports demonstrated elevated glutamate in glaucoma patients and in some glaucoma models (Brooks et al., 1997; Dkhissi et al., 1999; Dreyer et al., 1996), other groups did not observe glutamate elevation in similar settings (Carter-Dawson et al., 2002; Honkanen et al., 2003).

Immune component is also present in glaucoma (Tezel, 2011). Upregulation of different components of immune system was found in glaucoma patients (Kuehn et al., 2006; Wax et al., 1998; Yang, 2004). Also in various animal models immune response was upregulated (Johnson et al., 2007; Steele et al., 2006). So called 'para-inflammation' – weak but persistent activation of immune system seem to be the case in glaucoma. Oxidized macromolecules stimulate resident immune cells including microglia and seem to stimulate para-inflammation (Xu et al., 2009).

5. Antioxidant therapies in neurodegenerative diseases: Rationales and precautions

As shown above, ROS and RNS could be regarded as 'key players' in pathologies of various neurodegenerative diseases. This leads to idea that antioxidant supplementation can be a reasonable therapeutic strategy in neurodegenerative disorders. One can imagine two major strategies to reduce nitrooxidative stress in these pathologic conditions (Uttara et al., 2009):

- 'upstream' to nitroxidative stress
- 'downstream' to nitrooxidative stress

'Upstream' antioxidant therapies would lead to reduction of ROS/RNS production. This could be achieved by chelating metals that catalyze generation of free radicals (like hydroxyl radical), inhibition of enzymatic reactions leading to generation of ROS/RNS or its precursors (e.g. hydrogen peroxide or nitric oxide). 'Downstream' antioxidant therapies would include agents reducing or preventing inflammation but also direct antioxidants, i.e. 'antioxidants' in traditional and narrow meaning. Some examples of antioxidants are listed in table 1.

	Mechanism of action	Examples
Upstream antioxidants	Preventing formation of free radicals	- Chelators - Inhibitors of oxidases - Inhibitors of nitric oxide synthase - Antagonists of glutamate receptors - Calcium antagonists - Anti-inflammatory drugs
Downstream antioxidants	Scavenging free radicals (direct antioxidants)	- Tocopherols - Flavonoids - Selenium-containigs compounds (e.g. ebselen) - Polyenes (carotene, lycopene, retinol)
	Catalizing decomposition of free radicals	- Mimetics of superoxide dismutase and/or catalase (e.g. tempol)
	Preventing secondary burden by ROS/RNS	- Creatine - Carnitine - Lipoic acid - Nicotinamide - N-butyl-α-phenylnitrone

Table 1. Examples of upstream and downstream antioxidants.

Many of the known antioxidants were tested in various animal models of neurodegenerative diseases and some of them were also tested in clinical trials (see reviews by (Moosmann & Behl, 2002; Tan et al., 2003; Uttara et al., 2009)). It is hard to summarize this data but one has to admit that outcomes are somehow disappointing. Theoretically, the best we can expect in case of antioxidant therapy in neurodegenerative diseases is cessation of degenerative processes. This means that we can count on stopping the process that is normally already pretty advanced, in many diseases the first symptoms appear only when 40-50% of cells are lost.

Another lesson from these numerous studies concerns features which should characterize an antioxidant that could be potentially protective in neurodegenerative diseases. Ability to cross the brain-blood barrier (BBB) seems to be the crucial one (Gilgun-Sherki et al., 2001).

Many of the known antioxidants have poor ability to cross BBB. The way the molecule crosses BBB can be also of importance, e.g. vitamin C is transported as its oxidised form, dehydroascorbic acid, by glucose transporter and then reduced back to ascorbic acid. However, reducing dehydroascorbic acid consumes glutathione. This means that vitamin C supplementation would not lead to increase in the net cerebral antioxidant capacity (Tan et al., 2003).

There are some issues and controversies concerning antioxidant therapies *per se*. For years antioxidants used to be shown unequivocally as safe and widely applicable drugs. However, recent clinical trials suggest more careful approach to antioxidant application. In some cases they can even potentiate the damage (Halliwell, 2000; Salganik, 2001). One of the many possible reasons is that ROS and RNS are not only damaging agents but as mentioned before also play a vital signalling role in the cell. Cells and organisms maintain redox homeostasis and too low levels of ROS and RNS can also be detrimental. Potential side-effects of antioxidants are summarised in fig. 7.

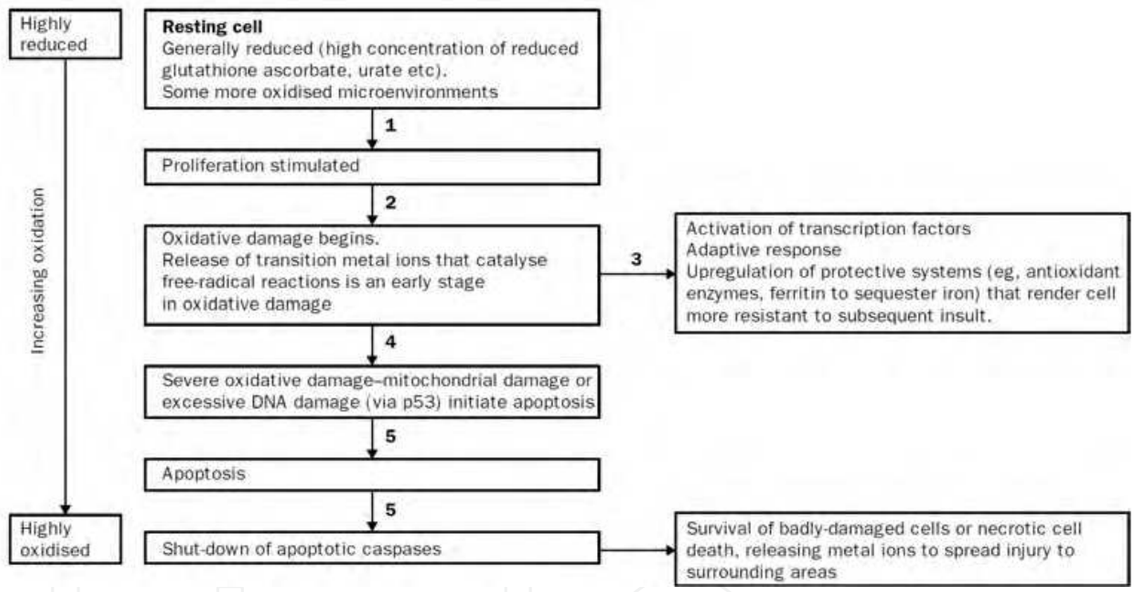


Fig. 7. Potential side-effects of antioxidants. Antioxidants might: (1) inhibit cell proliferation by preventing transient oxidations that stimulate protein phosphorylation and transcription factors; (2) protect against oxidative damage by scavenging excess ROS/RNS; (3) prevent adaptation to oxidative damage by decreasing transcription-factor activation; (4) accelerate oxidative damage by reducing transition-metal ions into their lower oxidation states that are better promoters of free-radical damage; and (5) inhibit free-radical-induced apoptosis, either beneficial to the organism or deleterious. Reproduced from Halliwell (2000).
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Good examples illustrating are mimetics of SOD, e.g. TEMPOL and other nitroxides, stable radicals that convert superoxide radical to hydrogen peroxide. Administration of substances that would help in eliminating superoxide radical seems to be a good therapeutic strategy and proved to be effective in many settings (Wilcox, 2010). On the other hand deleterious effects of SOD overexpression are well known, as they have been demonstrated in many

settings including cell lines (Groner et al., 1986) and transgenic animals (Avraham et al., 1988; Ceballos-Picot et al., 1991). Increased oxidative stress in Down's syndrome seems to be associated with SOD-1 overexpression (Sinet, 1982). Dose-dependency curve for SOD and also its mimetics in different experimental settings is 'bell-shaped', i.e. after reaching maximum protective effect further increasing the dose leads to decreasing the protective effect (McCord, 2008).

6. Conclusions

Nitrooxidative stress seems to be not only a common phenomenon in various neurodegenerative disorders, but also a common mechanism of neurodegeneration. Obviously, there are 'disease-specific' factors that activate and inter-play with nitrooxidative stress but neurodegenerative diseases seem to share some factors that are 'key players' in their pathology: excitotoxicity, mitochondrial disruption and neuroinflammation.

Antioxidant supplementation seemed to be an excellent therapeutic and prophylactic strategy for various neurodegenerative disorders. Recently, antioxidant supplementation occurred not as safe as we previously thought. Also efficacy of these therapies is somehow controversial. Perhaps we need antioxidants that are precisely 'targeted' and evaluate accurate dosing of these substances.

7. References

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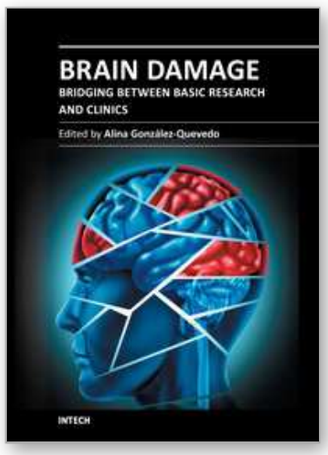
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"Brain Damage - Bridging Between Basic Research and Clinics" represents a collection of papers in an attempt to provide an up-to-date approach to the fascinating topic of brain damage in different pathological situations, combining the authors' personal experiences with current knowledge in this field. In general, the necessary link between basic and clinical neurosciences is highlighted, as it is through this interaction that the theoretical understanding of the pathophysiological mechanisms can be successfully translated into better ways to diagnose, treat and prevent the catastrophic events that occur when the brain suffers from external or internal noxious events. The book spans different aspects of brain injury, starting from damage occurring in the fetal and child brain, followed by different neurodegenerative processes. Attention is also focused on the negative effects of drug addictions and sleep deprivation on the brain, as well as on the early assessment of brain injury for preventive strategies employing sensitive biomarkers.

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