

# Oxidative stress and neuroregenerative processes – pathophysiological correlations and new pharmacotherapeutic approaches in the treatment of neuroregenerative diseases

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## Abstract

The aims of the current study are estimation of the correlations between oxidative stress and neuroregenerative processes and new pharmacotherapeutic approaches in the treatment of Parkinsonism. The investigation has been made through the existing electronic database of medical sources. Oxidative stress arises from an increased production of reactive oxygen/nitrogen species (ROS/RNS) or from a failure of the body's antioxidant defenses, characterized by a reduced ability of endogenous systems to combat the oxidative attack directed at target biomolecules. It is broadly defined as a lack of balance between the levels of reactive oxygen/nitrogen species (ROS/RNS) and the body's ability to counteract their effect through antioxidant defence systems. Free-radical induced attack has been associated with the onset of numerous health conditions such as neurodegenerative diseases (Parkinson's, Alzheimer's, Huntington's and amyotrophic lateral sclerosis), cardiovascular and inflammatory diseases. In addition, the irreversible progression of oxidative deposition caused by reactive oxygen species (ROS) leads to accelerated biological aging, blocked biological functions, and overall. Other risk factors for neuroregenerative processes are glutamate toxicity, autoimmune, protein aggregation, inflammation. The most severe motor neuron degenerative illness is Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's disorder).

## Keywords

Oxidative stress, neuroregenerative processes, parkinsonism, Alzheimer's disease

## Oxidative stress

Oxidative stress underlies the pathogenesis of aging and a number of diseases. The brain is particularly sensitive to the effects of free radicals due to high oxygen consumption, the presence of unsaturated fatty acids, and

reduced activity of oxidation-sensitive endogenous antioxidant systems. In Alzheimer's disease, oxidative stress occurs as a result of a disturbance in the balance between endogenous or exogenous overproduction of reactive oxygen species and a decrease in antioxidant defence mechanisms <sup>[1]</sup>.

## General Characteristics of Oxidative stress

Free radicals have high reactivity due to the presence of unpaired electrons in their structure. Free-radical processes damage intracellular, extracellular and membrane biomacromolecules: proteins, lipids, nucleic acids (DNA, RNA), thereby interfering with the transmission of intracellular signals, leading to the formation of toxins, tissue damage, alteration of the redox state of cells and cell death (apoptosis). Reactive particles are the cause of pathogenetic changes and the development of pathological processes in many diseases [2].

Oxidative stress results from an imbalance between the body's antioxidant defense mechanisms and the increased formation of reactive species: superoxide, hydroxyl, hydroperoxyl, alkoxy, peroxy, peroxyxynitrite radicals [2].

Research in the field of coordination compounds is directed towards the design of metal complexes of various biologically active organic ligands, which have practical applications in medicine and pharmacy in the therapy of various diseases. Oxidative stress underlies the pathogenesis of aging and in the etiology and neurodegeneration in neurodegenerative diseases such as Huntington's, Alzheimer's, and Parkinson's diseases, Lowe-Gerich (amyotrophic lateral sclerosis), multiple sclerosis and is the cause of the progression of schizophrenia, depression, autism, attention deficit hyperactivity disorder and chronic fatigue syndrome. Oxidative stress was first characterized by Sies as "a disturbance in the prooxidant and antioxidant balance that leads to potential damage. It is broadly defined as a lack of balance between the levels of reactive oxygen/nitrogen species (ROS/RNS) and the body's ability to counteract their effect through antioxidant defence systems [1]. Oxidative stress arises from an increased production of ROS and/or RNS species or from a failure of the body's antioxidant defenses, characterized by a reduced ability of endogenous systems to combat the oxidative attack directed at target biomolecules. Free-radical induced attack has been associated with the onset of numerous health conditions such as neurodegenerative diseases (Parkinson's, Alzheimer's, Huntington's and amyotrophic lateral sclerosis), cardiovascular and inflammatory diseases. In addition, the irreversible progression of oxidative deposition caused by reactive oxygen species (ROS) leads to accelerated biological aging, blocked biological functions, and overall, reduced life span [3].

## Reactive oxygen species (ROS) and reactive nitrogen species (RNS)

Reactive oxygen species (ROS) (or also called free radicals) were first described by Fenton in 1894. Intensive studies in this direction give us important information. In the cells of aerobic organisms, free radicals are most often generated

from molecular oxygen. It is characterized by the presence of two unpaired electrons with parallel spins in the outer electron shell. Due to this fact, one-electron reduction processes, which do not require spin inversion, are much more likely than two-, three- and four-electron reduction processes [4].

During the pathogenesis of Parkinson's disease (PD) [5] the production of oxygen-reactive species damages the substantia nigra through lipid peroxidation, protein oxidation, and DNA oxidation [6]. This phenomenon seems to be induced mainly by changes in the iron content of the brain, mitochondrial dysfunction [7], monoamine oxidase (MAO) activation, or even by changes in the antioxidant defense system [5]. Much evidence still indicates that exposure to dopaminergic neurotoxins may trigger PD-related pathology [8]. One of the ways is the effectivity of the oxidizing astrocytic. Another factor is the multiple detrimental oxidative reactions along with the possibility of the formation of reactive oxygen species, including superoxides ( $O_2^{\cdot-}$ ) in cellular mitochondria and the additional mitochondrial dysfunction and fragmentation along with the oxidative neuronal damage [5]. In addition, it should also be considered that in Parkinson's disease the dopaminergic neurons are extremely susceptible to oxidative stress [9], due to the various oxidants formed from the oxidative changes caused to dopamine after its release from the synaptic vesicles, including  $H_2O_2$  [10],  $O_2$  and hydroxyl (OH) and DA-semiquinone radicals' formation [4].

In healthy dopaminergic neurons, levels of ROS are strictly controlled by various antioxidative mechanisms involving glutathione (GSH), superoxide dismutase (SOD) and DJ-1. These processes, however, tend to fail in patients with PD.

Unfortunately, the current treatments for PD do not decrease the extent of neurodegeneration, which determines the necessity of the development of new compounds and approaches to novel therapies. Thus, proper agents decreasing the radical's formation and/or affecting the uncontrolled monoamine oxidase type B effectivity would be a promising strategy in the search for new antiparkinsonian agents.

The most common ROS in a biological system are:

- Superoxide anion ( $O_2^{\cdot-}$ ) - forms in electron-transport chains and is the precursor of a large number of ROS species. It does not reach far from the site of formation and is deactivated after the addition of another electron and two protons to produce hydrogen peroxide, or by cytosolic and mitochondrial superoxide dismutase [4].
- Hydrogen peroxide ( $H_2O_2$ ) - reactive and important for the progression of free radical processes, but is not a free radical. However, in the presence of  $Fe^{2+}$  or other transition valence metals it forms a hydroxyl radical ( $OH^{\cdot}$ ) [10]
- Hydroxyl radical ( $OH^{\cdot}$ ) - the most reactive of all ROS and a likely initiator of chain reactions leading to the formation of lipid peroxides and organic radicals.

They exist for a very short time and lead to severe oxidative damage. Can arise from a superoxide anion in the presence of hydrogen peroxide (Haber-Weiss reaction) [4]

- Organic peroxy radical ( $\text{ROO}^\cdot$ ) - formed after reactions of an oxygen molecule with carbon-based radicals. Peroxy radicals with carbon-based radicals. Peroxy radicals are significantly more stable than alkoxy-derived radicals ( $\text{RO}^\cdot$ ) and have a half-life of 7 seconds at 37°C. Organic hydroperoxides ( $\text{RCOOH}$ ) are not radicals but unstable and reactive products of peroxy radicals [4]

In addition to oxygen, highly reactive forms of nitrogen exist, the most common being nitric oxide ( $\text{NO}^\cdot$ ) and peroxynitrite anion ( $\text{OONO}^\cdot$ ).  $\text{NO}^\cdot$  is formed by the conversion of L-arginine to citrulline in the presence of nitric oxide synthase (NOS), while  $\text{O}^{2-}$  and  $\text{NO}^\cdot$  are required for peroxynitrite production. A dynamic equilibrium between the formation of reactive oxygen species and the function of protective antioxidant systems (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase) has been established in the body [4].

## Antioxidants

Antioxidants are substances that neutralize free radicals and remove or reduce their harmful effects. The main types of antioxidants are endogenous and exogenous. Endogenous ones are synthesized in the body [11]. The most important endogenous antioxidant is glutathione. It is synthesized from three amino acids - glutamine, glycine and cysteine. Glutathione reduces oxidative stress extremely well and has a strong detoxifying effect, improving liver function [12]. Exogenous antioxidants are those that the body cannot synthesize and must obtain through diet, supplements or intravenous therapy. This group includes the antioxidants vitamins C, A and E, the elements zinc and selenium and the biologically active compounds of the bioflavonoid and carotene groups [13].

The best studied antioxidant enzyme systems in the body by which free radicals are eliminated are:

1. superoxide dismutases (SOD) containing different co-factors: Cu-SOD, Zn-SOD (eukaryotes, humans), Fe-SOD (bacteria and chloroplasts), Mn-SOD (mitochondria) and Ni-SOD (prokaryotes) [14].
2. heme-containing enzyme catalase (CAT)
3. glutathione peroxidases (GPx): seven isoenzymes such as in humans are GPX1-GPX5
4. glutathione reductase (GR)

SOD is one of the first defense mechanisms against ROS and catalyzes the conversion of superoxide radicals to oxygen and hydrogen peroxide [14]. The generated hydrogen peroxide is converted to water and oxygen by CAT. Gluta-

thione peroxidase reduces hydrogen peroxide and hydroperoxides to water and alcohols and glutathione disulfide (GSSG), which is reduced to glutathione (GSH) [12] by the enzyme glutathione reductase.

Peroxiredoxins and the recently discovered sulfiredoxin are also enzymatic antioxidants. Other enzymes that have antioxidant properties, although this is not their primary role, include paraoxonase, glutathione-S transferases [15], and aldehyde dehydrogenases [11].

The nonenzyme group includes glutathione (GSH) [12], the most abundant antioxidant in most brain cells, thioredoxin (Trx), vitamins A, E, and C, and selenium. GSH reacts with ROS to generate glutathione disulfide (GSSG) and enters into a cycle with GPx and GR. The hydroxyl radical ( $-\text{OH}$ ) is bound by the endogenous antioxidants glutathione (GSH) and melatonin. Peroxynitrite ion  $-\text{ONO}_2^-$  and hypochlorite ion  $-\text{OCl}^-$  are bound by glutathione [11].

## Antioxidants against neurodegenerative diseases

Oxidative stress underlies the pathogenesis of aging and a number of diseases. The brain is particularly sensitive to the effects of free radicals due to high oxygen consumption, the presence of unsaturated fatty acids and reduced activity of oxidation-sensitive endogenous antioxidant systems [11]. In Alzheimer's disease, oxidative stress occurs as a result of a disturbance in the balance between endogenous or exogenous overproduction of reactive oxygen species and a decrease in antioxidant defence mechanisms. The study of the sequence of amino acids in A $\beta$ 42-peptides allows the specification of their precursor. Its abnormal degradation leads to the formation of A $\beta$ 42-peptides, which are involved in amyloidogenesis and neurotoxic adhesive amyloid peptides: 90% A $\beta$ 40-peptides and 10% A $\beta$ 42-peptides [16].

The hallmark of neurodegenerative diseases such as Alzheimer, Huntington, Lou Gehrig, Lewy body dementia, multiple sclerosis, and mitochondrial disorders as Friedrich's ataxia and Leber's neuropathy, is the progressive malfunction of the nervous system accompanied by atrophy of the structure or function of neurons or the death of neuronal cells [17]. The pathogenetic mechanisms of progressive neurological degeneration of the central nervous system are: mitochondrial disorders [18], oxidative stress [19], aggregation of proteins [20], membrane damage, and apoptosis [17].

Beta-amyloid [21] and alpha-synuclein fragments, as well as hyperphosphorylated tau protein, make up the majority of neurofibrillary tangles in Alzheimer's disease, or senile plaques [21]. The main strategies for prevention and treatment of Alzheimer's disease include drugs against amyloid plaques, hyperphosphorylation of tau protein and antioxidants [22]. Antioxidants are of great importance due to it has been reported that they exhibit properties to eliminate of reactive oxygen species [23].

Amyotrophic Lateral Sclerosis is the most severe degenerative disease of the upper and lower motor neurons. Amyotrophic Lateral Sclerosis (Charcot disease) [24] is characterized with the severest motor neuron disfunction. Bulbar signs, such as dysarthria (speech disorder) and dysphagia (swallowing difficulty), appeared in the latter stages of the illness. Risk factors are genetic mutations, oxidative stress, glutamate toxicity, lack of trophic growth factors, autoimmune-mediated attack, protein aggregation, inflammation, cytoskeletal abnormalities; viral infection [24]. Riluzole is important for treatment of Amyotrophic Lateral Sclerosis [25].

Antioxidants are an important additive therapy in treatment of the mentioned neurodegenerative diseases. It has been reported that antioxidant effect exert Vitamins A and E, amino acids, plant extracts, omega-3 unsaturated fatty acids.

Vitamins A and E are lipophilic molecules and important antioxidants of the group of fat-soluble vitamins acting against lipid peroxidation. Vitamin C (ascorbic acid) is one of the most important water-soluble antioxidants. Selenium is a crucial cofactor for the enzymes GPx and thioredoxin reductase (TrxR). All together act and balance the levels of ROS and RNS.

The flavanol epigallocatechin-3-gallate is the most abundant catechin found in green tea (*Camelia sinensis* L.) and, due to its antioxidant properties, suppresses cognitive impairment by reducing amyloid-induced mitochondrial dysfunction and neurotoxicity. Isothiocyanates (Moringine) have been isolated from representatives of Brassicaceae (Brussels sprouts, cauliflower and broccoli) and are sulfur-containing phytochemicals with protective effects in neurodegenerative diseases due to antioxidant and anti-inflammatory properties [26].

The following amino acids exhibit antioxidant effect: L-Arginine, L-Histidin, L-Isoleucine, L-Serine, L-Tryptophan and L-Tyrosine. The sulphur-containing amino acids L-Cysteine, N-Acetylsuccinate, L-Methionine, Taurine also possess antioxidant activity. N-Acetylsusteine has antioxidant properties that alleviate symptoms of depression and improve brain function, memory, and the ability to acquire new cognitions in the aged. Contained in garlic extract, S-allyl-L-Cysteine suppresses pathological cascades associated with synaptic degeneration and neuroinflammatory pathways [27].

Taurine is an antioxidant that provides magnesium and calcium access to brain cells and stimulates nerve cell function. Phosphatidylserine exhibits antioxidant activity in lipid peroxidation and activates enzyme activity and membrane function of nerve cells and is particularly effective when combined with Omega-3 unsaturated fatty acids.

Protective antioxidant effects in Alzheimer's disease are exerted by extracts of *Melissa officinalis* L. (Caffeic acid, Ferulic acid, Rosmarinic acid), *Rosmarinus officinalis* L. (Carnosic acid, Ferulic acid, Rosmarinic acid, Hesperidin), *Salvia officinalis* L. (Carnosic acid, Rosmarinic acid), *La-*

*vandula angustifolia* L., *Daucus carota* L., *Hypericum perforatum* L. (Quercitrin), *Withania somnifera* (stimulates superoxide dismutase, catalase and glutathione peroxidase activity) [26].

Some alkaloids show a trend of efficacy in the treatment of behavioral symptoms, with proven neuroprotective properties in experimental models of Alzheimer's disease: Galantamine, Nicotine, Morphine, Caffeine, Berberine, Huperzine [26].

Galantamine is appropriate for therapy of treatment of Alzheimer [28] due to exerts antioxidant and neuroprotective effect [29]. In the experiments, the antioxidant activity of Galantamine hydrobromide was investigated in vitro using a Luminol-dependent chemiluminescence method. Galantamine exerted a neuroprotective effect by lowering oxidative neuronal damage by binding reactive oxygen species:  $-O_2^-$  (superoxide),  $-O_2^{2-}$  (peroxide),  $-OH$  (hydroxyl),  $RO-$  (alkoxy) [29].

Omega-6 unsaturated fatty acids: linoleic,  $\gamma$ -linolenic, arachidonic (eicosatetraenoic) are grouped as vitamin F and contained in vegetable oils. Linoleic acid is the main representative of Omega-6 unsaturated fatty acids, present in nuts, seeds and vegetable oils. Omega-6 unsaturated fatty acids in small doses are necessary, but in large amounts counteract Omega-3 unsaturated fatty acids, even if Omega-3 unsaturated fatty acids are taken in sufficient amounts. Omega-3 unsaturated fatty acids reduce inflammation by inhibiting the conversion of arachidonic acid to proinflammatory factors; by suppressing other proinflammatory cytokines: tumor necrosis factor  $\alpha$ -interferon,  $\gamma$ -interferon, interleukin 1 (IL-1), IL-2, IL-1 $\beta$ ; by limiting T-cell proliferation and inhibiting leukocyte migration. Omega-3 unsaturated fatty acids may directly limit pathology in AD [30].

## Conclusion

Oxidative stress is a risk factor for the development of neurodegenerative diseases such as Parkinson's, Alzheimer's, Huntington's and Amyotrophic Lateral Sclerosis. An important role in prevention and treatment of neurodegenerative diseases. are antioxidants as Vitamins A and E, flavonoids and alkaloids from plant extracts, aminoacids, omega-3 unsaturated fatty acids.

Plant extracts from *Lavandula angustifolia* L., *Melissa officinalis* L., *Rosmarinus officinalis* L., *Salvia officinalis* L., *Hypericum perforatum* L., *Withania somnifera* are described to possess antioxidant activity and can help for protection against Alzheimer's disease. Galantamine is appropriate for therapy of treatment of Alzheimer due to exerts antioxidant and neuroprotective effect. Drug Riluzole exhibits effects against different diseases due to protects against memory loss, has antidepressant-like qualities, and is used to treat chronic schizophrenia, autistic disorder, Parkinson's disease, and hereditary ataxia as an adjuvant therapy to Risperidone.

## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

### Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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