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Novel Approaches of Oxidative Stress Mechanisms in the Multiple Sclerosis Pathophysiology and Therapy

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Abstract: It is suspected that the development of multiple sclerosis (MS) can be affected by oxidative stress (OS). In the acute phase of the disease, OS is responsible for initiating inflammation, whereas in the chronic phase it sustains neurodegenerative process. Redox processes in MS are related to dysregulation of axonal bioenergetics, cerebral iron accumulation, mitochondrial dysfunction, impaired oxidant/antioxidant balance, and OS memory. This chapter gives an overview of the role of OS in MS.

Key words: Antioxidants; Antioxidative enzymes; MS biomarkers; Multiple sclerosis; Oxidative stress

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Introduction

Multiple sclerosis (MS) is a multifactorial disease of the central nervous system (CNS), characterized by inflammation, demyelination, and axonal loss. MS is considered a biphasic disease with inflammatory relapsing-remitting (RR) and degenerative secondary progressive (SP) phases (1). The ultimate causative factors of these processes remain unknown. Emerging evidence suggests a role for oxidative stress (OS) in demyelination (1–3). This chapter summarizes the role of OS in the pathology of MS and the potential of oxidant scavengers as therapeutics for the treatment of MS.

Mechanisms of OS

An imbalance between the production of free radicals and the antioxidative defense leads to OS and nitrosative stress (4, 5). Free radicals are defined as unstable, short-lived, and highly reactive molecules - containing one or more unpaired electrons in the valence shell or the outer orbit.

As a result of the high reactivity, free radicals can abstract electrons from other molecules which lose their electron and the molecule becomes a free radical itself, initiating a chain reaction cascade which finally damages the living cell (4). Free radicals, that is, the reactive oxygen species (ROS) and reactive nitrogen species (RNS), may have an influence on crucial classes of biological molecules, which results in multiple lipid and protein damage due to peroxidation and nitration processes (4, 6). ROS and/or RNS are involved in many essential physiological functions such as immune regulation (i.e., defense against pathogens), mitogenic response, cellular signaling, and redox regulation (4, 7). Both ROS and RNS can be grouped into two subgroups: radicals and nonradicals (4, 8) (Figure 1). Superoxide radical, hydrogen peroxide, hydroxyl radical anion, nitric oxide (NO), and peroxynitrite are thought to be involved in the development of MS (8, 9). The superoxide radical exists in two forms: superoxide and hydroperoxyl radical anion. It is mostly produced in the mitochondria. Under physiological pH, superoxide is the most common ROS that reduces iron complexes such as cytochrome c and ferric ethylene diaminetetraacetic acid, and oxidizes ascorbic acid and tocopherol (4). The hydroperoxyl radical can easily enter the phospholipid bilayer of cell membranes (4).

The enzymes that can produce superoxide include xanthine oxidase (10), lipoxygenase, cyclooxygenase (11), and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent oxidase (12). Hydrogen peroxide is formed *in vivo* in a dismutation reaction catalyzed by superoxide dismutase (SOD). It can cross biological membranes and damage DNA by forming hydroxyl radical, which can react with organic and inorganic molecules (13). It is formed during the Fenton reaction, between hydrogen peroxide and metal ions (Fe or Cu). It is often bound to ferritin and ceruloplasmin or other molecules. Under stress conditions, the superoxide anion radical releases free iron from ferritin. The released free iron participates in the Fenton reaction to form the hydroxyl radical (4).

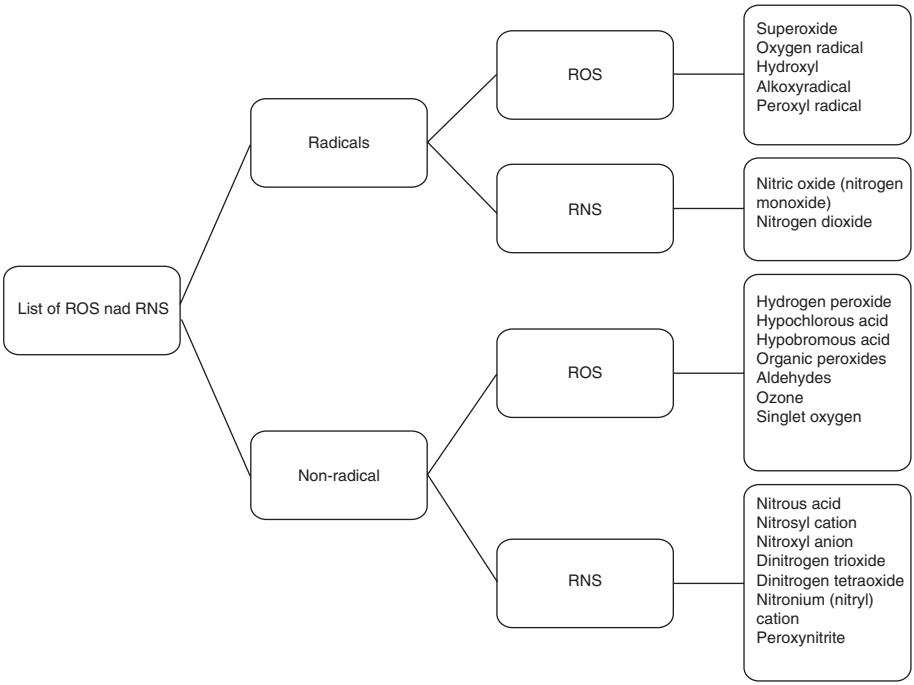

Figure 1 Reactive oxygen species (ROS) and reactive nitrogen species (RNS) (5, 9–11). The classification of ROS and RNS depended on having an unpaired electron. Nonradial species exists without an unpaired electron.

Nitric oxide is produced by nitric oxide synthases (NOSs). NOS isoforms include neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS). NO is a crucial intracellular second messenger involved in many biological activities such as blood pressure regulation, smooth muscle relaxation, neurotransmission, cellular defense, and immune regulation (4). Peroxynitrite, which is a very toxic compound, is formed during the reaction between superoxide radical and NO (nitrogen monoxide) (14), with subsequent new reactive compounds (nitroso-peroxo-carboxylate or peroxynitrous acid) leading to oxidation of lipids, proteins (methionine and tyrosine), and DNA (15).

The Mitochondrial Dysfunction Theory in MS

Mitochondria play a significant role in synthesizing adenosine triphosphate and providing energy to the cells. They possess their own DNA and are genetically independent organelles. Moreover, they are involved in apoptosis and metabolism of fatty acids (16–18). An oxidative energy metabolism is required for the lifespan of neurons while the large amount of adenosine triphosphate is produced during oxidative phosphorylation. In this reaction, the greatest amount of

harmful ROS and RNS is formed. In the case of the disturbed mitochondrial antioxidant production, the following are observed: decreased adenosine triphosphate synthesis, impaired Ca^{2+}, and elevated ROS and RNS (16, 19). Mitochondrial dysfunction plays a particular role in inflammatory processes. In the case of mitochondrial dysfunction, an overproduction of toxic ROS and RNS is observed (20). It plays a pivotal function in myelin and oligodendrocyte loss which is detrimental to neurons and glia (14, 21). Mitochondrial disturbances cause many neurodegenerative processes, including DNA damage, insufficient mitochondrial enzyme activity, abnormal mitochondrial gene expression, and defective DNA repair mechanism (22). As a result, mitochondrial damage in MS was considered to play an important role in disease progression (23, 24).OS leads to mitochondrial damage, thus disrupting transport of adenosine triphosphate along axons, resulting in neurodegeneration (25–27). Faulty mitochondrial DNA was reported as the consequence of oxidative and nitrosative stress (28). It was found that peroxynitrite, superoxide, and NO can destroy mitochondria in experimental autoimmune encephalomyelitis (EAE) and inhibit aconitase, creatine kinase, manganese, and SOD. These reactions lead to increased mitochondrial proton permeability, damage to mitochondrial DNA, and lipid peroxidation (29). In addition, recent findings in EAE suggest that mitochondrial dysfunction occurs in the early stage of MS (30). Interestingly, mitochondrial damage seems to develop before the inflammatory process in the disease (31). Mitochondria have a variety of antioxidant enzymes, including antioxidants peroxiredoxin-3 and thioredoxin-2 as well as their regulator *PGC-1*α. Increased astrocytic *PGC-1*α in active MS lesions might be an endogenous protective mechanism to reduce oxidative damage. Activation of *PGC-1*α represents a promising therapeutic strategy (32).

Inflammatory Mediators and Antioxidants

New findings suggest that chemokine 11 (CCL11) in the serum and in the cerebrospinal fluid (CSF) released from activated astrocytes promote OS via microglial NOX1 activation and glutamate-mediated neurotoxicity. These findings proposed using inhibitor of NOX1 in therapy (33, 34). The modulation of glutamate release and transport may also become a new therapeutic target (35). Another study explained how tumor necrosis factor-alpha (TNF-α) inhibits the accumulation of progenitor cell differentiation. It depends on a number of factors such as increased ROS production, altered mitochondrial calcium uptake, mitochondrial membrane potential, and respiratory complex I activity. The accumulation of progenitor cells at the lesion sites is observed in MS patients (36) and suggests that failed remyelination is a consequence of the inhibition of differentiation (37). In another study, authors presented the possibility of using a *TNFR2* agonist as a factor protecting microglia against OS (38). Enhanced astrocytic peroxisome proliferator–activated receptor gamma coactivator1-alpha (*PGC-1*α) levels reduce the production of pro-inflammatory mediators such as IL-6 and chemokine (C-C motif) ligand 2, and antioxidant enzymes such as peroxiredoxin-3 and thioredoxin-2, in human primary astrocytes. Activation of *PGC-1*α may be a protective factor for neurons (32).

The results from the study of Andaloussi et al. presented the use of exosomes, biologically active nanovesicles (30–120 nm) that can be easily delivered across the blood–brain barrier (BBB) (39), to increase remyelination post-injury. They stimulated primary dendritic cell cultures with a low level of IFNγ. Exosomes (IFNγ-DC-Exos) contain microRNA species which are involved in oligodendrocyte development pathways and can increase baseline myelination, reduce OS, and improve remyelination. IFNγ-DC-Exos also increased oxidative tolerance, antioxidant levels, and anti-inflammatory miRNAs. Furthermore, IFNγ-DC-Exos, nasally administered to animals, increased CNS myelination *in vivo* (40).

Such therapy may involve supplementation of melatonin which can scavenge the hydroxyl, carbonate, alkoxyl, peroxyl, and aryl cation radicals, and stimulate the activities of antioxidative enzymes (GPx, SOD, etc.). Oxidative process may also be inhibited by NOS (41). It was reported that melatonin (10 mg daily/30 days) caused a statistically significant increase in antioxidative enzymes such as SOD and GPx and a decrease in malondialdehyde (MDA) in erythrocytes of SPMS patients (42). However, the relationship between the Expanded Disability Status Scale (EDSS), Gd + and SOD concentration in erythrocytes in clinically isolated syndrome (CIS) and RRMS patients is not clear and requires further investigation (42, 43). Melatonin also plays an important role in improving the antioxidant defense in MS through upregulation of sirtuin1 (*SIRT1*) and its target genes for MnSOD and CAT (44). Moreover, melatonin is selectively taken up by mitochondrial membranes, which makes it a potential therapeutic tool in treating neurodegenerative disorders (45).

Genetics seems to play a significant role. The GSTP1 polymorphism and quinone oxidoreductase 1 (NQO1) variant genotypes in MS patients suggest that a defective function of detoxification enzymes could be a determinant of susceptibility and the clinical presentation of the disease (46, 47). α(alpha)-lipoic acid (ALA) is a natural, endogenous antioxidant that acts as a peroxisome proliferator–activated receptor-γ (*PPAR-γ)* agonist to counteract OS (48, 49). Another data provided the first evidence that ALA may increase the production of *PPAR-γ in vivo* in EAE and may reveal antioxidative and immunomodulatory mechanisms for the application of ALA in humans with MS (48).

Emami Aleagha et al. indicated that a decreased concentration of Klotho, an antiaging protein, in the CSF of patients with RRMS showed a significant negative correlation with the EDSS and a positive correlation with total antioxidant capacity (TAC). Klotho concentrations may play an important role in the regulation of the redox system (50). Glutathione is an antioxidant in the brain which might be a marker of the oxidative line of defense in MS patients and might serve to monitor the disease progression (51). Furthermore, an impaired iron metabolism plays a major role in the pathogenesis of MS (4). In the saliva of patients with MS, ferric reducing ability (FRA) was reduced by 38% as compared to the control. The same study also demonstrated a decrease in the antioxidant status in the serum such as TAC (52). A study on 30 female patients showed lower TAC levels and higher TOS levels compared with the controls indicating a decreased endogenous antioxidants and increased OS (53). Another study showed that an expression of antioxidant power such as plasmatic FRA and thiol group dosage was significantly lower in patients with active disease (54).

Ferroxidase (FeOx) activity of ceruloplasmin prevents OS by promoting the connection of free radicals from iron ions to transferrin. A reduced serum FeOx

activity was noted in 69 RRMS patients and in 62 patients with other inflammatory neurological disorders (55). Serum uric acid (UA) concentrations in 30 MS patients and 20 controls with noninflammatory neurological diseases support the significance of UA in the pathogenesis of MS. Serum UA concentrations were found to be significantly lower in MS patients as compared to the controls (56). Recent reports indicated that urine aMT6s levels significantly correlated with MS functional composite score but not with the EDSS. These authors believe that there might be some new hope in developing a quantitative and objective measure to assess the severity of MS (57).

Antioxidants: Enzymatic and Nonenzymatic

Antioxidants, which are divided into enzymatic and nonenzymatic, are substances that protect the body against free radicals (Table 1). Among enzymes, the most important include catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), SOD, serum paraoxonase, arylesterase (53), and δ-aminolevulinate dehydratase (δ-ALA-D) (48). SOD has three isoforms, namely, copper/zincSOD (SOD-1), manganeseSOD (SOD-2), and extracellular EC-SOD (58). It needs to be stressed that in serum, the major antioxidant enzymes that can eliminate the hydrogen peroxide include CAT, GPx, and peroxiredoxins (4). Furthermore, glutathione-S-transferases (GSTs) and nitrite reductase NAD(P)H quinone oxidoreductase 1 (NQO1) are detoxifying enzymes that prevent cells from oxidative

TABLE 1 The Types of Antioxidants

Enzymes Oxidants (28, 46, 47, 51, 55)	Nonenzymatic Antioxidants (12)	
CAT	Low molecular weight antioxidants	Antioxidant elements
GPx	Uric acid	Ions: Cu, Fe, Zn, Mn
GR	Vitamin C	
SOD	Vitamin D	
Paraoxonase	Vitamin E	
Arylesterase	Glutathione	
GSTs	Coenzyme Q	
NQO1	B-carotene	
Peroxiredoxin-3	AU	
Thioredoxin-2, 6		
FeOx		
δ-ALA-D		

The types of antioxidants depend on molecular structure. The table lists the most important barrier antioxidant enzymes and other compounds and ions which are not enzymes.

CAT = Catalase, GPx = Glutathione peroxidase, GR = Glutathione reductase, SOD = Superoxide dismutase, GSTs = Glutathione-S-transferases, NQO1 = NAD(P)H:quinone oxidoreductase1, FeOx = Ferroxidase, δ-ALA-D = δ Aminolevulinate dehydratase, UA = Uric acid.

damage (46). The concentration of these enzymes in serum may reflect the status of an antioxidant line of defense.

Nonenzymatic antioxidants may be classified into low molecular weight and antioxidant elements (ions). Low molecular weight antioxidants include UA; vitamins C, D, and E; glutathione; coenzyme Q; and b-carotene (9). Other tissue antioxidants include ceruloplasmin and ferritin. Iron (Fe), copper (Cu), zinc (Zn), and manganese (Mn) are the most important ions with antioxidant properties. The general and nonprotein thiol groups represent a nonenzymatic segment of the antioxidant defense system (59). The total glutathione and reduced glutathione can be assessed in the serum and are substrates for enzymes such as GPx and GR (60). UA is a natural nonenzymatic endogenous antioxidant, neutralizing overproduction of peroxynitrite (9).

The Importance of OS in MS

The inflammatory component in the course of MS is significant not only due to neuronal and axonal loss but also due to the initiation of the degenerative cascade in MS in the early stage (2). The activation of microglia and macrophages constitutes a major factor responsible for the production of ROS (8) due to high oxygen consumption (2, 4). Microglia activated by T-lymphocytes release proteolytic enzymes, cytokines, oxidative products, and free radicals. However, microglia also have many protective properties (61), such as neuroprotection, lowering of inflammatory response, and stimulation of tissue repair (62). Neurodegeneration in the course of MS is influenced by two processes, namely, OS (63) and excitotoxicity. Pathomechanisms of excitotoxicity are associated with glutamate overload (16), calcium overload, ionic channel dysfunction, mitochondriopathy, proteolytic enzyme production, and activation of apoptotic pathways.

Interestingly, persistent hyperactivation of oxidative enzymes suggests an "OS memory" in chronic neuroinflammation (64). Dysregulation of axonal bioenergetics plays a significant role in OS and axonal injury (27, 65). CSF examination during the exacerbation of MS demonstrated a bioenergetic failure related to an increased mitochondrial proton leak as well as an increased expression of genes that are involved in oxidative damage (66). Furthermore, the presence of proinflammatory cytokines in the CSF and pro-oxidative markers (e.g., nitrotyrosine) leads to cytokine-induced synaptic hyperexcitability and also glutamate-dependent neurotoxicity (67, 68). Recently published studies stress the significant role of ceramides in the CSF as the signaling molecules causing mitochondrial dysfunction. Short-chain ceramides stimulate the production of OS and lead to neuronal death (69). Cerebral iron accumulation is also significant. This process causes chronic cell stress, contributing to axonal and neuronal death (70). The excessive accumulation of iron was detected in MS plaques. Extracellular hemoglobin oxidizes and leads to local OS by the globin radical which may be responsible for myelin basic protein oxidative cross-linking and heme involved in the peroxidation of lipids (71). Neurodegeneration is related to iron liberation from the myelin sheath at the time of demyelination (72). Diffuse neurodegenerative process is

connected with high iron concentration in the basal ganglia (73). Ferrous iron may intensify oxidative injury in the presence of oxygen radicals (74, 75). Mitochondrial injury, OS, and energy failure may be connected to the formation of plaques and neurodegeneration in white and gray matter lesions (17, 76). Neurodegeneration in the course of MS is related to chronic subclinical extravasation of hemoglobin into lesions, the dysfunction of various cellular protective mechanisms against extracellular hemoglobin reactivity, and OS (77). Another study stressed that changes in the oxidant and/or antioxidant balance played a role in the pathophysiology of the disease. Attention was paid to the balance between the concentration of compounds such as lipid peroxidation levels; carbonyl protein content; DNA damage and SOD; CAT activities; vitamins E and C; and nonprotein thiol content (78). Also, the presence of free radicals in the nervous tissue may be toxic; for example, peroxynitrite increases the inflammatory response, thus leading to such a high concentration in the chronic phase that it may result in neurodegeneration (9).

The Impact of Antioxidants on the Course of MS

OS at each stage of MS is a key element in the pathogenesis of the disease. At the time of relapse, all these processes are intensified, leading to neuronal loss. Current treatment is focused on decreasing inflammation, but not on preventing neurodegeneration. It is possible that a new target of treatment will focus on neutralizing free radicals. The course of the disease is affected by the use of antioxidants and substances that affect antioxidant pathways that reduce the severity, cause faster remission, and result in less pronounced course of neuroinflammation and neurodegeneration (79). The process, known as "remote damage," may have a significant effect on neurodegeneration. This process can damage neurons functionally related to the primary focus. The therapeutic window that occurs between the primary and secondary damage can be used to implement new neuroprotective treatment (80).

New Possibilities in the Treatment of MS—Neuroprotection

A number of substances have been tested for a possible ability to protect the brain against neurodegeneration; however, the identification of neuroprotective drugs has been problematic (2). The limited response to the application of ROS scavengers results from their short half-life, in the order of milliseconds, and the degree of instability of ROS (61, 81, 82). Hydralazine may become a potential therapy due to the fact that it protects cells from the damaging effects of acrolein (61, 83, 84). The following agents could offer help in preventing mitochondrial dysfunction and in improving neurodegeneration: CDDO-ethyl amide, CDDO-trifluoroethylamide, pioglitazone, rosiglitazone, resveratrol, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), and bezafibrate (85).

Other findings suggest that neural stem cells (NSCs) exposed to 125 μM H_2O_2 for 30 min, and pretreated with different doses of lovastatin for 48 h, were protected

against OS-induced cell death by the expression of *PGC-1*α, which is a master regulator of mitochondrial function controlling energy metabolism and *Nrf2*. It is possible that in the future lovastatin may be used to promote the survival rate of NSCs (86). The compounds that can readily cross the BBB include:simvastatin, atorvastatin, cerivastatin, pravastatin and rosuvastatin (87). Exendin-4 and GLP-1 have been shown to reduce inflammation, demyelination and cytokine release in various animal models of MS (88). Most glucagon-like peptide-1 (GLP-1) mimetics such as exendin-4, liraglutide, and lixisenatide cross the BBB and show neuroprotective effects in many studies. However, further studies are needed to clarify the relationship with OS.

Polymerized form of nano-curcumin (PAP) has been shown to exert anti-inflammatory and antioxidative effects, and also repair myelin in EAE, a mouse model of MS (89). Nontoxic inhibition of myeloperoxidase may restore the BBB integrity and limit migration of myeloid cells into the CNS (90). The antioxidant protein peroxiredoxin 6 (PRDX6) can reduce the inflammation in the CNS and potentiate oligodendrocyte survival (91).

The Relationship between Immunomodulatory Therapy, OS, and Antioxidants

Immunomodulatory therapies protect from relapses whereas corticosteroids treat relapses. However, their effect is only partial and further search for new therapeutic options is needed. The transcription factor *Nrf2* is a key regulator of antioxidative defense (92, 93). Oral dimethyl fumarate (DMF) activates anti-inflammatory and antioxidative pathways to upregulate the expression of this molecule (94, 95). A differential expression is involved in the defense against OS, predominantly in actively demyelinating white matter lesions (58, 94, 96).

DMF and monomethyl fumarate (MMF) activate Nrf2 transcriptional pathways (97). Target genes of *Nrf2* include heme oxygenase-1, glutamate cysteine ligase transcription factor1, and NAD(P)H oxidoreductase-1. Furthermore, MMF impedes the activation and migration of lymphocytes; however, it does not have an impact on the function of macrophages. It is a potential novel mode of action differentiating this drug from other immune-modifying drugs (98). It was also shown that therapies aimed at stimulating endogenous antioxidant pathway, for example, the induction of the Nrf2 pathway, may demonstrate positive effects in a situation of moderate OS such as the one in the classical EAE models (27). On the other hand, they might be counterproductive in the case of extensive oxidative injury; it has been proposed that the amplification of oxidative injury in MS is only minimal in the studied rodent models (99).

T-cell-secreted IFNγ stimulates OS and demyelination in MS. However, induction of physiological levels of IFNγ protects against demyelination and OS. Therefore, it is important to apply phasic and pulsed IFNγ to the brain (100). Combination therapy with immunomodulatory drugs antioxidants, for example, IFN-β and glatiramer acetate, significantly reduced TNF-α; however, it did not affect other ROS/NRS biomarkers or disease progression (101). In another study, the level of protein carbonyls was elevated in RRMS patients treated with interferon

β-1b and glatiramer acetate whereas, serum protein thiol groups were decreased; in the absence of immunomodulatory drug, the same markers of OS were significantly elevated (102). Sadowska–Bartosz et al. demonstrated an increase in oxidation parameters in serum of RRMS patients treated with IFNβ-1a and IFNβ-1b. However, this increase was less significant compared with untreated RRMS patients or SPMS patients treated with mitoxantrone (103). It should be borne in mind that mitoxantrone is associated with an increased level of OS (104). On the other hand, the study demonstrated that mitoxantrone did not have an effect on the activity of paraoxonase 1 (a type of enzyme that protects cells from OS) (104).

Arnold et al. evaluated the suicidal erythrocyte death induced by mitoxantrone. The study showed that mitoxantrone triggered cell apoptosis, partially due to the formation of ROS and ceramide, thus increasing OS. In addition, the authors assessed the effect of the antioxidant N-acetylcysteine, which significantly reduced the effect of mitoxantrone (105). Due to the fact that the studies are not conclusive, it appears that treatment with IFN-β and mitoxantrone does not reduce OS (103). Another study demonstrated that melatonin supplementation at a dose of 5 mg over 90 days resulted in a significantly decreased MDA concentration in IFN-β and glatiramer acetate–treated groups but not in the group treated with mitoxantrone. In turn, a significant increase in SOD activity was observed only in the group treated with glatiramer acetate as compared to the controls (106).

Interestingly, melatonin may also have implications for the treatment of severe MS. One of the studies indicated that the TAC level was significantly lower in the mitoxantrone-treated group, and it increased after melatonin supplementation (107). Therefore, a combined use of immunomodulatory therapies with antioxidants may prove beneficial. IFN-β and C-phycocyanin, a biliprotein from *Spirulina platensis* with antioxidant, anti-inflammatory, and cytoprotective properties, improved the redox status and ameliorated clinical deterioration of mice with EAE (108). Fingolimod reduced hyperoxia-induced OS, activation of microglia, and associated pro-inflammatory cytokine expression in neonatal oxygen-induced brain injury (109).

Attempts were also made to explain some of the beneficial effects of natalizumab and its antioxidant capacity. Researchers studied serum melatonin levels in 18 patients with RRMS treated with natalizumab and noted that it caused significant increases in serum melatonin concentrations (87). In one of the studies, 22 MS patients were assigned to the treatment with 300 mg of natalizumab. After 14 months, it was observed that natalizumab prompted a decrease in oxidative damage biomarker levels and induced nuclear translocation of *Nrf2*, which is responsible for the activation of the antioxidant pathway, and a fall in serum vascular cell adhesion molecule-1 levels (60). In addition, a decrease in carbonylated protein levels was found in patients with the highest levels of severity (EDSS>5) (110). To conclude, it appears that most of the drugs used in MS are directly or indirectly modulate OS.

Corticosteroids in Relapses—The Importance of OS and Antioxidants

The role of corticosteroids in OS is poorly understood. Wang et al. examined levels of MDA and TAC in peripheral blood and in the CSF of RRMS patients 7 days before

methylprednisolone (MP) treatment and 1 month after MP treatment. They found that the increase in OS markers precedes inflammatory response in MS patients and MP treatment reduces the neuroinflammatory attack by decreasing brain antioxidant enzymes (111). Ozone autohemotherapy is an emerging therapeutic technique that can change brain metabolism. It was shown that MS patients demonstrated a marked increase in cytochrome-c-oxidase (CYT-c) activity and concentration about 40 min after autohemotherapy, possibly revealing a reduction of the chronic OS level typical of MS patients (112) A protective effect of ozone (O3) therapy was reported in EAE in rats either alone or in combination with corticosteroids. Such a combination allows to reduce the dose of MP due to a decrease in the level of brain glutathione, paraoxonase 1 enzyme activity, brain MDA, TNF-α, IL-1β, IFN-γ, Cox-2 immunoreactivity, and p53 proteins (113). The study showed that adding compounds that modulate redox pathways in the cell could increase the effectiveness of the therapy and reduce the dose of corticosteroids.

Conclusion

The role of OS in MS is of great importance as it has a pivotal role throughout the duration of the disease. In the acute phase it initiates inflammatory processes and in the chronic phase it sustains neurodegeneration. Increased levels of OS markers and decreased levels of antioxidant molecules have been observed in patients with MS independently of the course of the disease. The use of antioxidants offers hope for a better prognosis, particularly in conjunction with immunomodulatory therapy and corticosteroids. MS patients may benefit from antioxidant supplementation.

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