Oxidative Stress and Neurobiology of Demyelination

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Abstract Despite a large amount of research which aims at defining the pathophysiology of human demyelination (i.e., multiple sclerosis), etiological bases of disease have been unknown so far. The point of intersection of all assumed etiological factors, which are mainly based upon immunological cascades, is neuroinflammation. The precise definition of the place and role of all pathogenetic factors in the occurrence and development of the disease is of crucial importance for understanding the clinical nature and for finding more effective therapeutic options. There are few studies whose results give more precise data about the role and the importance of other factors in neuroinflammation, besides immunological ones, with regard to clinical and paraclinical correlates of the disease. The review integrates results found in previously performed studies which have evaluated oxidative stress participation in early and late neuroinflammation. The largest number of studies indicates that the use of antioxidants affects the change of neuroinflammation course under experimental conditions, which is reflected in the reduction of the severity and the total reversibility in clinical presentation of the disease, the faster achieving of remission, and the delayed and slow course of neuroinflammation. Therapies based on the knowledge of redox biology targeting free radical generation hold great promise in modulation of the neuroinflammation and its clinical presentations.

Keywords Oxidative stress · Neuroinflammation

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Neuroinflammation

The central nervous system (CNS) is a very sensitive tissue for damages which has little capacity for regeneration [1]. Due to this fact, inflammation reactions, which are the pathophysiological basis for all CNS damages regardless of etiology, have, as a consequence, nervous tissue damages of different levels of manifestation and reversibility [2].

CNS tissue is an "immunologically privileged" part of an organism because of the existence of the blood-brain barrier (BBB) and the absence of the lymphatic system. The blood-brain barrier is a physical and transport barrier for toxic matter and cells which could invade the CNS [3, 4]. It is composed of two biological barriers. The first one is formed of tight junctions of endothelial cells of brain microcirculation; it contains multiple efflux pumps, which eliminate toxic and decomposing metabolic products from the CNS into the systemic circulation. The second one is formed of a basement membrane and astrocytic extensions which form the so-called glial membrane. For these reasons, the invasion of circulating cells into the CNS is conducted through two separate processes: (1) transendothelial migration into the perivascular space and then (2) infiltration of CNS parenchyma by passing through the glial membrane [5]. These two processes are regulated independently so that circulating cells can migrate only into the perivascular space without the possibility of passing into CNS parenchyma, if the glial membrane is morphologically and functionally intact [6].

Immunologically competent cells present in the CNS under physiological conditions are microglial cells. They represent the residential cell population of the CNS. The assumption is that they are created by the transformation of circulating monocytes and the cells of myeloid lineage which colonize the CNS during its embryonic and early neonatal development [7, 8]. Under physiological conditions, microglia forms an extensive network of long cellular extensions with a relatively

small cell body. Under pathological conditions, after the activation, microglia transforms into a phagocytic cell phenotype which causes the formation of many amoeboid protoplasmatic extensions like the ones formed by activated macrophages [9] (Fig. 1). Besides, activated microglia forms and secretes different proinflammatory cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide (NO·) by means of which it communicates with other cells of the CNS [10]. In the perivascular space, there physiologically exists a so-called subpopulation of inactive macrophages which, in a pathological sense, have a role of antigen-presenting cells, and thus, they activate a specific immune system [11]. Besides these cells, there are also rear T lymphocytes in charge of CNS protection, which enter the CNS parenchyma through transendothelial migration, by means of adhesion molecules present on the surface of endothelial capillary cells, but, without antigens and/or autoimmune pathology, they do not initiate immunological processes [12].

The inflammation process is initiated only in the state when there is an increased number of monocytes and T lymphocytes, delivered to CNS from the systemic circulation; when their transendothelial transport is facilitated and accelerated; as well as when there are antigens in the CNS on which T lymphocytes are sensitized by means of antigen-presenting cells [13]. Once the inflammatory process is initiated in the CNS, it is conducted like in any other organ in the further course of its propagation. There is an increased formation of molecular messengers which attract monocytes and lymphocytes, microglia multiplies, and the activation of the complement system is initiated and antibodies are created [14].

Immunological protection of the CNS is reduced in some of its parts, like the parenchyma, chambers, and meninges, so these parts could become the place of inflammatory reaction similar to the one occurring in other organs [2, 15]. On the other hand, the cortex is less suitable for infiltration compared to the white matter and the spinal cord [16]. The existence of different regional sensitivity to CNS inflammation could be a consequence of different histological structures, given that the cortex contains millions of neuronal bodies, which, in a way, achieve immunosuppressive effect by strengthening the BBB [17]. These biological features represent a contribution to understanding the existence of predilection places for the appearance of inflammation in the CNS.

BBB disruption, which exists in all the neuroinflammatory processes in varying degrees of manifestation, is a key mechanism by which a "protected" CNS tissue is exposed to the effects of activated cells of innate or acquired immunity. Therefore, determining the relation of albumin concentration in the CSF and serum, and MRI of the CNS with a paramagnetic agent such as gadolinium, chelated by diethylene triaminopentacetate (Gd-DTPA) in the form of a dimeglumine salt, which penetrates the CNS only if the BBB has been damaged, has an important role in evaluation of BBB damage severity, as well as the intensity of a neuroinflammatory process [18, 19].
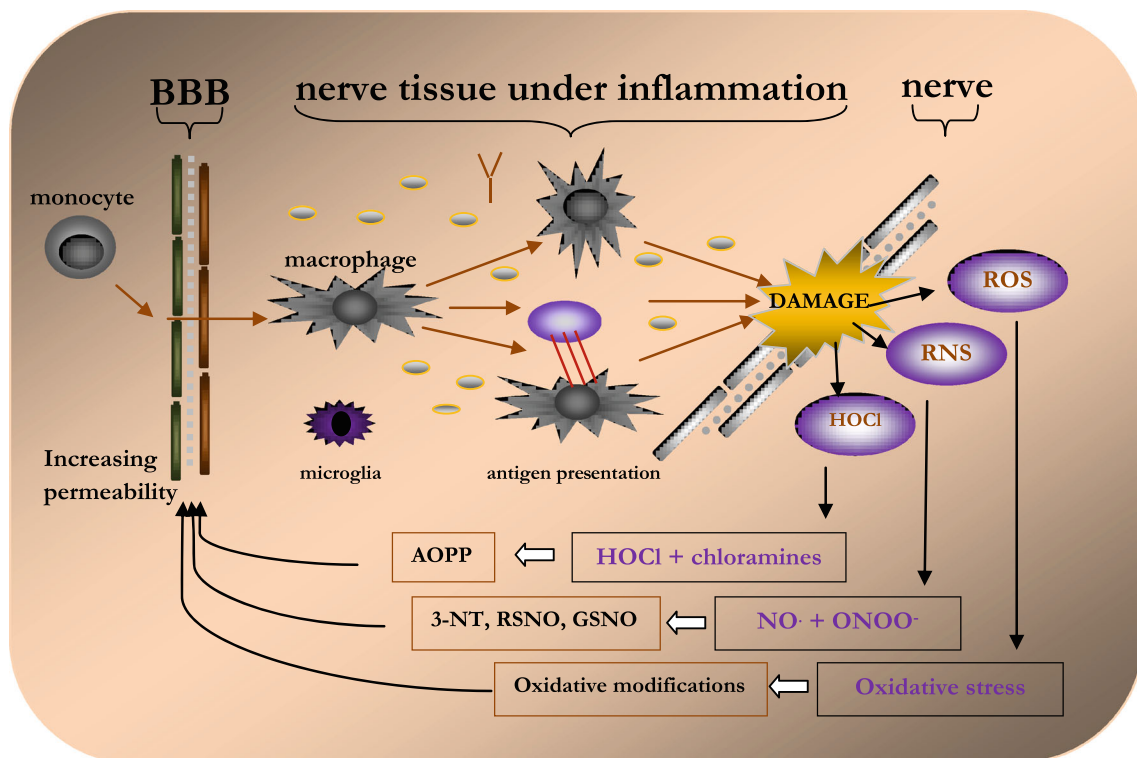
Fig. 1 The role of immune cells in the pathogenesis of neuroinflammation and demyelination

Oxidative Metabolism and Its Specificities in the CNS

Free radicals are atoms, molecules, or ions with unpaired electrons. They are created in biological systems because of breaking of covalent bonds in the process of homo- or heterolysis or by means of electron transfer. Due to exceptional chemical instability, free radicals enter chemical reactions with other free radicals and nonradical molecules. This makes them the leading pathogenetic link in many pathological conditions [20]. Free radicals are created in various conditions: during oxidative phosphorylation in mitochondria, in the process of phagocytosis, in the reactions of biotransformation of exogenous and endogenous substrata in endoplasmic reticulum, in enzymatic reactions which catalyze oxidases, in the process of eicosanoid synthesis, and in oxidoreduction reactions in the presence of metal with variable valency [21–30]. Lipid peroxidation occurs as a consequence of free radical secretion, even though during the very process of lipid peroxidation free radicals are being created in increased concentration. All reactive chemical species (radical and nonradical) can be oxygen species, reactive species of nitrogen, and carbon- and sulfur-reactive species [31–33].

Oxidative modification of proteins implies a covalent protein modification which is a consequence of the effect of reactive chemical species or the products of their interaction with other biomolecules. CNS diseases, primarily the ones based on a neuroinflammatory process, are conditions where these types of changes occur a lot [34]. Advanced oxidation protein products (AOPP) and advanced glycation end products (AGE) are considered exceptionally pathogenic due to the fact that they are generators of free radicals and independent promoters of the further spreading of the process of their uncontrollable production [35–40].

Lipid peroxidation is one of the most commonly studied processes of redox cell signalization disorders where free radicals play the key role. Through the different mechanisms, lipid peroxidation disrupts membrane barrier function, inactivates membrane enzymes, and increases permeability for water, monovalent and divalent ions, and often for high molecular weight compounds. Lysosomal membrane damage enables the exit of hydrolytic enzymes, while mitochondrial membrane damage leads to Ca ion release and the activation of enzymes dependent on this ion [40–49].

Oxidative stress is a pathological condition which implies overproduction of ROS under conditions when their elimination is reduced [50–60]. Under physiological conditions, owing to the efficiency of enzymatic antioxidative potential of the organism (superoxide dismutase (SOD), catalase, etc.) (Fig. 2) and nonenzymatic molecules (GSH, vitamin C, vitamin E, bilirubin, etc.), ROS concentration is low and then ROS manifest a series of useful physiological features. They imply the cell division and growth
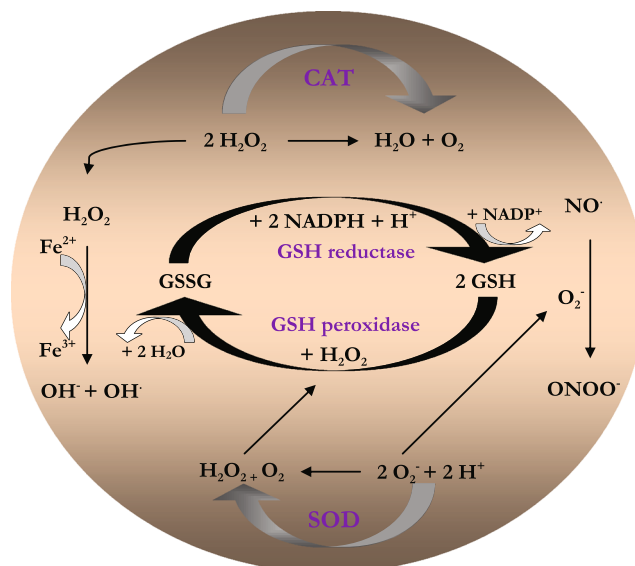
Fig. 2 The antioxidative mechanism

regulation, apoptosis regulation, oxidative modifications of biomolecules in extracellular space, protection from pathogen invasion, etc. [61]. Reactive oxygen species and products of their interaction with other biomolecules cause DNA mutations, ion channel damage, intensification of the lipid peroxidation process, and oxidation of proteins and other biomolecules [62, 63]. Under the conditions of oxidative stress, ROS can directly initiate a cascade of proinflammatory actions by stimulating cytokine production and BBB damaging and by enabling cells of the immune system to penetrate into the CNS [64]. On the other hand, the most important mediator in the described oxidative processes is $ONOO^-$, which is created as a product of NO and O_2^- reaction [65, 66].

CNS cells are exposed to low concentrations of ROS under physiological conditions, but due to the good antioxidative protection, their adverse effects are negligible [67]. CNS structures are particularly sensitive to ROS effects, which is a consequence of a highly activated metabolism of the CNS, when 2–5 % of the used O_2 is turned into ROS in the process of cell breathing in mitochondria [1]. ROS realize their effects in their immediate environment in relation to the place of their production, diffusing in the diameter of up to 0.3 nm. By comparison, the size of the interlaminar space of the myelin sheath is 10 nm.

On the other hand, the CNS has a relatively limited potential for anaerobic metabolism which makes it especially sensitive to hypoxia [68]. Under conditions of small O_2 availability, there is a dramatic increase of O_2^- concentration in mitochondria [4]. Finally, some CNS cells, like oligodendrocytes, for example, have a physiologically low level of antioxidative potential, as opposed to the relatively high energy turnover [69]. A high percentage of lipids in the CNS is the basis of its

tendency to initiate lipid peroxidation processes. It has been shown that the brain tissue is more sensitive to the described damages, in comparison to the tissue of the spinal cord or the peripheral nervous system [70]. This could be a consequence of the lower content of thiol redox system in the spinal cord and the peripheral nerves in comparison to the brain tissue [16]. The aforementioned differences are also related to the different GSH concentrations, taking into account that GSH participates in ROS reduction, but, on the other hand, it reactivates antioxidative enzymes in the CNS by means of independent mechanisms. GSH is mostly located in astrocytes (up to 5 mM), which is a lot more than in other CNS structures [71].

Oxidative Stress in Neuroinflammation

The mitochondrial respiratory chain, xanthine oxidase, NADPH oxidase, lipooxygenase, cyclooxygenase (COX), and nonenzymatic processes like dopamine and noradrenaline autooxidation appear as the main sources of ROS creation in the CNS. In oligodendrocytes, peroxisomes are an important ROS source because they are present in large numbers in the process of active myelination [72]. Microglial cells are an important source of ROS, under the conditions of neuroinflammation, as a consequence of their activation. Microglial cells are considered to be ROS depots under these pathological conditions and key initiators of the demyelination process which is ROS mediated. Peroxynitrite is important for macrophage activation due to the fact that it converts lipoproteins into forms which, independently of other factors, initiate phagocytic activity of macrophages because it binds to the so-called scavenger receptors of macrophages [9]. Neurons are also a source of ROS, given that ROS are created in the processes of electrical activity of a cell. It is assumed that transport of Ca into the axons, as well as Ca release from intracellular depots into the interior of the cell, is of greatest importance in this process. The intensive metabolism of axons under conditions of neuroinflammation is, at the same time, the explanation of the occurrence of their spontaneous, repetitive triggering in them, with the occurrence of corresponding clinical equivalents. This is followed by the increase of extracellular concentration of K, which simultaneously activates astrocytes, due to the fact that astrocytes are important for buffering extracellular changes in K ion concentration [72–77].

Some studies of demyelinating plaque have found the increased presence of LDL molecules, modified by lipid peroxidation, in the very plaques, macrophages, and astrocytes, in parallel with the increase of the concentration of lipid peroxidation end products [78–80]. This process leads to arachidonic acid release, which is enzymatically converted into prostaglandin or is converted to isoprostanes by nonenzymatic metabolism.

Isoprostanes are created by free radical lipid peroxidation of arachidonic acid, and among all isoprostanes, 8-epi-PGF2α is especially used as a biomarker of oxidative stress. Prostaglandins, especially E₂, independently or in conjunction with NO·, can increase BBB permeability [79]. However, prostaglandins are considered as conditional pathogens in neuroinflammation, due to the fact that their end product in the nervous tissue is dependent on the intensity of oxidative stress in the CNS [72, 81].

Oxidative stress in the CNS also causes changes in transendothelial transport which enables further evolution of the neuroinflammatory process [67, 82, 83]. The most important effect of ROS is damage of oligodendrocytes, which are the key cells in the process of myelin creation in the CNS. Even though the mechanisms of damaging of these cells are not completely clarified, it has been proven that oxidative stress and NO· have a very important role in that process [84]. There are studies which have shown that oligodendrocytes are sensitive to ROS concentrations much lower than toxic concentrations of other glial cells, astrocytes, and microglia. A protective effect on this cell line has been achieved by adding antioxidants [72, 85]. During the periods of myelin production and remyelination processes, the peroxisomal fraction of oligodendrocytes increases the volume and density, in accordance with metabolic requirements, thus representing an important independent ROS source [86–88]. Therefore, in the process of remyelination which is parallel to the process of active demyelination, oligodendrocytes are particularly predisposed to damage by means of oxidative stress [89]. In this way, altered MBP and PLP are more susceptible to trypsin degradation, which suggests that under in vitro conditions, myelin, being altered by oxidative stress, is easily subjected to degradation by the effects of extracellular protease, like the ones released by myelin [90]. Delamination of myelin sheath makes new amounts of myelin components prone to being damaged by ROS. ROS activity leads to the increase of concentration of mRNA and protein expression of matrix metalloproteinase (MMP-1), an interstitial collagenase which actively participates in the process of further demyelination [72, 91, 92].

Oligodendrocytes are especially sensitive to enormous release of glutamate, much more than astrocytes [93]. During acute attacks of the disease, concentrations of glutamate are increased which is, among other things, a consequence of inhibition of its takeover by astrocytes, resulting from the effects of proinflammatory cytokines, TNF-α, INF-γ, and IL-1β on astrocytes. Excitotoxicity of glutamate is mediated by the reduction of cystine concentration, which leads to the reduction of GSH concentration, too [94]. Oligodendrocytes in all their development forms, starting from the progenitor cell to the mature oligodendrocyte, have half the concentration of GSH in comparison to astrocytes. It is a consequence of the lower activity of glutathione synthetase, half the activity of

GR compared to astrocytes, and far lower activity (15 % of astrocyte activity) of GSH-Px. Immature oligodendrocytes are sensitive to oxidative damages compared to mature forms. Lower activity of SOD has also been shown in oligodendrocyte culture compared to microglial cells and astrocytes [72, 95, 96]. Oligodendrocytes contain the biggest amount of Fe which is otherwise located in the CNS [97]. In neuroinflammation, due to microglia activation, Fe can be released from depots, ferritin, and transferrin, and, under conditions of a lower activity of SOD, it can trigger oxidative stress. Fe deposits have been found during radiological examinations of MS patients [98, 99].

Pathogenetic Importance of Oxidative Stress Modulation in Neuroinflammation

The Importance of Modulating the Process of Lipid Peroxidation

One of the leading pathogenetic mechanisms which oxidative stress use to achieve its pathogenetic effect in neuroinflammation is the process of lipid peroxidation [100]. There are some studies which have found the increased intensity of lipid peroxidation in experimental autoimmune encephalomyelitis (EAE) [101], indicating that the intensity of this process could be a direct consequence of immunoinduction toward its own antigens of the myelin sheath which has a high lipid content [17]. The association of the loss of immunological tolerance toward its own antigens MBP and MOG and the increase of the products produced by means of malondialdehyde (MDA)-mediated covalent alteration of proteins and the interaction of MDA with cysteine, lysine, and histidine were proven in this way [102]. Some results indicate the direct relation between the increase of MDA concentration and the severity of EAE neurological findings [103] and the relation between the increase of MDA concentration and the radiological findings of MS patients [104].

Some studies have shown that the modification of albumin affected by MDA, during neuroinflammation, causes the initiation of the immune response toward this protein, along with the simultaneous activation of a specific immunity, which aggravates the course of neuroinflammation and the severity of its clinical manifestation [105, 106]. Recent studies indicate that the complement factor H, as the main MDA-binding protein, can block the initiation of this type of immunostimulation. The probable mechanism in the basis of this effect is the takeover of molecules modified by MDA activity by phagocytic cells, which prevents the loss of immunotolerance and, in that way, the adverse effects in the nervous tissue which could be initiated [107]. The reduction of the intensity of oxidative and nitrosative stress directly reduces the intensity of lipid peroxidation, along with the improvement of the clinical manifestation of neuroinflammation [108]. The effect of reducing the intensity of lipid peroxidation has been proven by other studies [108, 109], indicating that MDA could be a sensitive marker of neuroinflammation intensity [110].

Some results indicate that the increase of MDA concentration in plasma and CSF has been observed in different clinical phenotypes of neuroinflammation [79, 111]. There are results which point to the close relationship between the intensity of lipid peroxidation process and the concentration of proinflammatory cytokines [41], indicating the decline of the intensity of this process along with a reduction of the intensity of the inflammatory reaction [112]. This effect has been observed after the use of corticosteroid therapy, wherein the larger decline of MDA concentration has been in the plasma than in the CSF [48]. The increase of MDA concentration in the CSF is a direct consequence of the increased intensity of lipid peroxidation process in the CNS during neuroinflammation, which obviously exists during the clinical remission of the disease. This is supported by the finding of the increased MDA concentration in the CSF after stabilization of the BBB by the use of corticosteroid therapy, which suggests that the increase of MDA concentration in the CNS is not a consequence of an "overflow" of this biomarker from the periphery through BBB damage, due to the fact that a high level of MDA is also reflected after therapeutic stabilization of the BBB [48]. This finding has been supported by the results of recent studies which indicate the larger increase of MDA concentration in the CSF than in the plasma in MS patients [104]. For this reason, the level of MDA in the CSF is considered to be the marker which directly reflects the intensity of neuroinflammation, especially due to inverse correlations of MDA level and the volume of the intact nervous tissue, which has been proven in neuroinflammation [113].

Taking into account that lipid peroxidation is a common link for the activity of nitrosative and oxidative stress [46, 114], it is considered as the crucial pathogenetic mechanism in the process of neuroinflammation and the nervous tissue damages mediated by it [115]. There are some results which indicate the absence of difference in MDA values in CSF and plasma between the patients with different clinical phenotypes of neuroinflammation [104]. The majority of end products of lipid peroxidation are taken from plasma or CSF by macrophages or they are being bound to the proteins of CSF or plasma [45]. In this way, MDA can be absorbed through the arachnoid villi into the blood, which reduces its concentration in CSF at the expense of increasing the concentration in plasma [61], which could be the explanation for the absence of any difference in MDA values in CSF and plasma between different clinical phenotypes of neuroinflammation [104].

It has been shown that erythrocytes of the patients suffering from autoimmune diseases [77, 116], including the ones

suffering from MS, show greater rigidity of the cell membrane and the tendency toward spontaneous and induced cell lysis, which is in direct correlation with the intensity of inflammation [117] and its clinical presentation [118, 119]. It has been proven that the basis of these processes is the increased intensity of lipid peroxidation, taking into account that the erythrocyte membrane is a suitable substrate for initiating this process under conditions of the increased nitrosative and oxidative stress, which exist in neuroinflammation [41, 45, 100]. Similar results have been found by some of the recent studies [120, 121] which also indicate the existence of positive correlations between the process of lipid peroxidation and paraclinical findings of neuroinflammation. The authors found the explanation of the obtained correlations in the increased concentration of the products produced by the covalent modification of different biomolecules by the effect of intermediate and end products of the process of lipid peroxidation. These products, important for the further pathogenetic mechanisms of neuroinflammation, also include the advanced oxidation protein products (AOPP) [24, 122, 123].

Pathogenetic Aspects of the Role and Importance of AOPP in Neuroinflammation

Since the very discovery of AOPP, it has been defined as a stable marker of oxidative modification of protein [124], which was also confirmed by some of the recent studies [100]. The increased concentration of AOPP under conditions of oxidative and nitrosative stress is not surprising considering the fact that proteins, in accordance with their concentration which is larger than other biomolecules in the organism, are the primary target of ROS [99, 100].

The production of AOPP is explained by the chemical interaction of chlorine oxidants (chloramine and hypochlorite), which are abundantly produced in neuroinflammation, and proteins [18, 125]. However, it has been proven that AOPP are not only the end products of such chemical interaction, but, after creation, they also have a role as active mediators in the further evolution of the inflammatory process. AOPP realize their pathogenetic importance in neuroinflammation by the induction of the production of various cytokines and adhesion molecules which are important for the process of increasing BBB permeability [126]. Taking into account that AOPP are created by the effect of chlorine oxidants produced by nonspecific immune cells, which are the first line of defense in neuroinflammation, they could be considered as indicators of the intensity of the earliest inflammatory reaction [127]. This statement is supported by the finding of the positive correlation between the value of AOPP in CSF and plasma in MS patients and the parameters of the biological-biochemical syndrome of inflammation, primarily the number of leukocytes, the concentration of CRP, and fibrinogen [128].

Oxidatively modified proteins are hydrophobic and subject to denaturation, fragmentation, and aggregate formation with other oxidatively modified biomolecules [129]. In accordance with the fact that they are formed from proteins, AOPP could be considered as the direct marker of the content of albumin and the total proteins in a given tissue. However, the confirmation of such assumptions has not been obtained by the results of some recent studies because AOPP concentration in the CSF has been larger in patients with a smaller CSF content of proteins [128]. Taking into account the aforementioned facts, it seems that other proteins, not only albumins, though being the main protein fraction of plasma and CSF, participate in the formation of AOPP. In their work, Heinecke and associates [130] performed an analysis of the connection between AOPP concentration and other markers of protein damage and showed the direct connection with serum concentration of dityrosine which is considered to be a marker of oxidative stress intensity in general, while a far weaker connection was observed between AOPP concentration and other products of protein modification [131]. Similar results have been found by other studies which have analyzed the electrophoretic finding of AOPP, wherein the existence of two different peaks has been observed, of 670 and 70 kDa [130]. It has been shown that the peak of the higher molecular weight is formed by the aggregates of oxidatively modified albumins which mostly form disulfide bonds, as well as dityrosine aggregates, while the peak of the lower molecular weight contained albumins and other plasma proteins in a monomeric or structurally modified form.

Even though, on one side, AOPP are more susceptible to proteolytic degradation, and on the other side, they are taken over in slight quantities by phagocytic cells, which leads to the increase of their extracellular concentration [53, 125]. In accordance with this, higher AOPP values in patients with neuroinflammation suggest the existence of intensive inflammatory processes, which is confirmed in some studies of the parameters of the biological-biochemical syndrome of the inflammation of these patients [128].

During neuroinflammation, AOPP can directly perform the increase of the expression of transcriptional factors and cytokines, like NF-κB, TNF-α, iNOS, and some adhesion molecules like ICAM-1 and VCAM-1, which are considered to be of crucial importance in the inflammatory processes of the CNS and the induction of the immune response on the whole [132, 133]. On the other hand, preservation of defense capacities is necessary so that the nervous tissue and the whole organism could react as a response to this stimulus [134]. Over time, during the course of the disease, defense mechanisms become exhausted, which is, to some extent, present even during periods of clinical remission [83]. Therefore, the increased AOPP concentration, which indicates a more intensive inflammatory cascade, causes a higher level of nervous tissue damage and thus a more severe clinical picture of

neuroinflammation only under conditions of disrupted defense potentials of the organism [135, 136]. Even though positive correlations between AOPP concentrations and the clinical finding and the length of MS were observed [137, 138], while interpreting these findings, AOPP concentration was not of crucial importance, but it was the disruption of defense mechanisms [137], because the effect shown by AOPP in relation to myelin and axon damage was potentiated in the group of patients with longer duration of the disease [128].

It is assumed that in the interaction with myelin sheath, AOPP is directly involved in the process of neoepitope creation, which leads to immunoinduction and favoring of further damaging of the nervous tissue [126]. AOPP can also have a direct immunogenic effect in the CNS by means of the products of the incomplete proteolytic degradation [129]. Starting form this statement, the existence of morphological changes in the brain tissue in MS patients, seen by radiological examination [129], could be understood as a consequence of this effect of AOPP on the nervous tissue [139].

The results of the earlier studies show the increased concentration of oxidatively modified proteins in erythrocyte membranes under conditions of oxidative stress [47]. There is some evidence of the direct link between the erythrocytic content of AOPP and MDA and the severity of the clinical manifestation and the length of neuroinflammatory condition [20, 139, 140].

The Damaging of GSH Homeostasis and the Level of SH Groups in Neuroinflammation

Considering the higher concentration, and thus the greater importance, in comparison to other redox-regulating molecules in the cell, GSH concentration changes have been studied in many prooxidative conditions [56, 141, 142]. The results of these studies agree with the conclusion that the decline of GSH concentration is responsible for the evolution of oxidative damages and the occurrence of their clinical correlates.

The decline of GSH concentration and its increase after the use of a substance which realizes the modulatory effect on the intensity of the nitrosative and oxidative stress have shown a negative correlation with the severity of EAE clinical manifestations [99]. Due to the fact that GSH synthesis in neurons is directly dependent on the concentration of the existing GSH and cysteine availability, it is not surprising that GSH declines in EAE, when GSH is spent due to the buffering of redox oxidative disbalance, and that it increases after the use of N-acetylcysteine (NAC) which is the direct donor of cysteine. Similar results have also been published in some other studies [143]. The takeover of cysteine is mediated by the cystine/glutamate transporter which is expressed on the BBB and other CNS structures [144]. Due to the fact that this process

mediates the injection of cystine into the cell in contra-transport with glutamate, the activity of this transporter is reduced under conditions of disruption of the gradient of the extracellular concentration of the glutamate which initiates this process. The disruption of this gradient exists in neuroinflammation. The increased expression of this glutamatergic transporter, EAAT1, in brain tissue of EAE animals [104] confirms the existence of glutamatergic excitotoxicity. In this way, glutamatergic excitotoxicity leads to the disruption of the antioxidative capacity of the CNS [145, 146].

Special sensitivity of oligodendrocytes to the oxidative damages is caused by the physiologically lower content of GSH [147, 148]. Other glial cells activated in neuroinflammation because of high GSH concentrations show a higher level of resistance to the nitrosative and oxidative damages [149]. There are studies which indicate that the supplementation of the precursors of GSH synthesis increases the resistance and the regenerative ability of oligodendrocytes [148]. This effect is probably mediated also by the prevention of glutamatergic excitotoxicity, which is confirmed by the reduction of the expression of the EAAT1 transporter in the brain of EAE animals treated with NAC [104, 128].

There are results which indicate that the use of NAC directly reduces TNF-α expression and thus the cell damages mediated by it [148–150]. This mechanism of NAC effect lays in the basis of NO· concentration decline in EAE animals treated with NAC, due to the fact that the reduction of TNF-α also reduces its direct stimulatory effect on iNOS activity [151, 152]. Some studies indicate that thiol supplementation prevents cell death mediated by the activation of ASK1 complex, also known as apoptosome, which reduces cell damages in the CNS [153], the consequence of which is the benign clinical presentation of the disease. The increased production of NO· during inflammation is important for the process of GSH consumption in the CNS [154]. In the direct interaction of NO· and GSH and other low molecular weight antioxidants, S-nitrosoglutathione (GSNO) and S-nitrosothiols (RSNO) are created [142, 155]. In this way, the thiol content is reduced and the redox oxidation buffering capacity of the CNS is directly modified [156, 157]. RSNO is mostly created by means of GSNO, wherein NO· from GSNO moves to the protein thiol groups [158, 159]. In this way, GSNO increases bioavailability of NO· and participates in the regulation of NO· depots in the CNS and the regulation of nitrosative stress intensity [160, 161]. GSNO achieves its effect in the process of degradation to NO· and GSSG in the reaction which is spontaneous or mediated by low molecular weight thiols [161]. GSH concentration decline under conditions of NO· overproduction is, among other things, conditioned by the overproduction of RSNO [104, 118]. On one hand, NO·-mediated damages could be prevented in this way [162–164], but since NO· can be further released from RSNO,

which can multiply its concentration, its adverse effects could also be potentiated [161, 165]. There are results which indicate that RSNO can also manifest independent immunogenic features, which contribute to the intensification of the inflammatory processes in the CNS [166]. The results of some studies indicate the presence of antibodies on RSNO, or the products of its interaction with other biomolecules, in the plasma or CSF of MS patients [167].

The special importance of thiol redox system in the CNS is in the process of cell signalization in the CNS and in the process of CNS growth and development and control of cell death [143]. As a part of signal pathways in the CNS, produced RSNO is important for the balance of the activities of many enzymes, like S-nitrosoglutathione reductase, thioredoxin reductase, Cu/Zn SOD, carbonyl reductase, and protein disulfide isomerase [129, 157]. RSNO can also mediate S-nitrosylation of the p65 subunit of NF-κB, which inhibits translocation of this transcriptional factor into the nucleus, and thus potentiate the antiinflammatory effect [168]. On the other hand, it is known that proinflammatory cytokines, TNF-α, IFNγ, and IL-1b, lead to demyelination of the p65 subunit, thus intensifying the inflammation process [169]. It seems that the interaction between GSH and NO· is another important place in neuroinflammation pathogenesis where nitrosative and oxidative stress converge. There are results which show that RSNO produced in such way performs covalent modification of all isoenzymatic forms of NOS, thus reducing their activity and disabling the production of new quantities of NO· [170]. In this way, controlled production of NO· is achieved, and that is why the RSNO amount could be the direct indicator of NOS activity [161, 171].

GSH concentration reduction in neurons of MS patients leads to actin polymerization and rearrangement of these filaments, which is confirmed by the histological finding of the analyzed demyelinating plaque. ATP quantity is reduced in this process, which further potentiates prooxidative processes and damages created by their activity [142]. There are results which indicate that the level of GSH concentration declines, which is the consequence of its consumption during the buffering of redox oxidative damages and RSNO formation, which is confirmed by the results of the experimental [172] and clinical research [128]. In the research of Prasad et al. [173], GSH treatment has not shown the protective effect in relation to the intensity of the process of neuroinflammation and its clinical correlates. On the contrary, GSH concentration decline and RSNO concentration increase had an important effect on the reduction of the intensity of inflammatory processes in the CNS, also affecting the reduction of its clinical manifestation [173]. The assumed mechanisms of these effects seem to be the consequence of the overrated role that NO·, released from RSNO, can participate in the processes of posttranslational modification of different signal molecules important for the process of neuroinflammation [174, 175].

The decline of GSH concentration in erythrocytes during the acute attack of MS was shown in some of the earlier studies [176]. There are results which indicate that the antioxidative supplementation based on the large amount of thiol potentiates the increase of antioxidative capacity of erythrocytes [177]. The decline of GSH concentration is interpreted by the accelerated consumption with the aim of compensating the prooxidative condition which exists in these cells [178]. This is supported by results which indicate a negative correlation between the decline of intracellular concentration of GSH, the intensity of oxidative and nitrosative stress, and the length of this state [179].

Under in vitro conditions, it has been shown that the inhibition of inflammation caused by lipopolysaccharides increases the intracellular content of thiol [180]. The assumed mechanism of such effect could be S-nitrosylation of free GSH which modulates the activity of Th17 cells, whose effects are independent of Th1 and Th2 cell response [181]. In this way, a protective effect is achieved on the appearance, the course, and the clinical manifestation of neuroinflammation.

While the content of nonprotein thiol is important for the cell antioxidative capacity, numerous protein SH groups are important components of the antioxidative capacity of the plasma and CSF [163]. These SH groups, as well as SH groups of the cell membrane, are the suitable substrates for the activity of ROS of various alkylation agents, which leads to the reduction of their concentration and the loss of the role they have in the organism [182]. There are results which show the decline of the total SH groups in plasma and CSF in both CIS and RRMS groups [128]. Results of other studies also indicate the decline of total SH group concentration in MS patients during the relapse of the disease, with the increase of SH group concentration after corticosteroid therapy and the establishment of clinical remission [48]. Calabrese et al. [183] point to the big pathogenetic importance of the reduction of SH group concentration in the acute inflammation of the nervous tissue. In the studies of Scapagnini et al. [184], it has been shown that the use of different antioxidants prevents the loss of the total quantity of SH groups. It is assumed that this effect is achieved by modulating the intracellular signalization by the stimulation of HSP32 and heme oxygenase-1, which are the key factors in the earliest phases of neuroinflammation. The reduction of the intensity of neuroinflammation and oxidative and nitrosative stress after the use of interferon therapy leads to the increase of SH group concentration, with the simultaneous improvement of clinical findings [133, 185]. However, there are studies with a larger number of included patients which do not find such a correlation of the changes in SH group concentration and the clinical findings [83].

It has been shown that restoring GSH levels via supplementations based upon thiols could be less effective if GPx

activity is impaired [186]. There is evidence that GPx activity approached significant decreased values in MS compared to values obtained in control subjects [22, 187]. There are results which demonstrate that some drugs, being evaluated for therapy in MS, suppress inflammatory activation caused by lipopolysaccharides in vitro, enhancing total thiol levels. That was mediated by distinct mechanisms which were partly dependent on GSH-related enzymes, but other than GPx [180]. There is also a report that states that mitoxantron therapy induces the marked decrease in GPx activity in MS patients, after its initial elevation, which is followed by significant amelioration of clinical severity [188]. There are reports which suggest that both enzymatic and nonenzymatic antioxidants could regulate the function of immunologic cells enrolled in neuroinflammation and its promotion [189]. GPx can act as an inhibitor on 5-lipoxygenase in monocytes and macrophages within inflammatory-mediated processes, in this way decreasing the intensity of neuroinflammation, since 5-lipoxygenase is highly induced in the named inflammatory cells [190].

Pathogenetic Aspects of the Change in Catalase and Superoxide Dismutase Activity in Neuroinflammation

Catalase (CAT) is the main part of the brain antioxidative response [55, 57]. It is an intracellular antioxidant enzyme mainly located in cellular peroxisomes and cytosol which has been found in all cell types of the CNS, including also oligodendroglia which are particularly vulnerable to the effects of oxidative injuries [191]. Some authors demonstrated that various CAT treatment protocols might be useful in suppressing MS progression under experimental [86, 192] and clinical [193] conditions. Lower CAT activity in MS patients might be a consequence of the insufficiency of CNS antioxidative responses due to disease duration [48]. Thus, the CAT activity can be influenced by the limitation of GSH bioavailability, since it is well known that CAT activity is especially important in case of GSH depletion, which is demonstrated in MS [25]. Calabrese et al. [148] demonstrated an approximately threefold increase of CAT activity in the CSF of MS patients compared to control values. Considering CAT activity inducement in disease protection, there is also a demonstration of amelioration of experimental demyelization induced by combining scavenging of superoxide and hydrogen peroxide by viral-mediated gene transfer of the human CAT gene [55]. The findings by van Horssen et al. [21] demonstrate that antioxidative enzymes, including CAT and SOD, are markedly upregulated in active demyelinating MS lesions.

The changes of the activity of SOD in neuroinflammation are expected due to the fact that SOD represents the first line of antioxidative defense of the organism [26, 29, 53]. In the CNS, Cu/ZnSOD (SOD_1) is highly expressed in astrocytes, MnSOD (SOD_2) is expressed in neurons, while the

extracellular Cu/ZnSOD (SOD_3) is characterized by a decreased expression compared to the previous two SOD isomorphs [26]. The results of the studies which have tested SOD_1 activity changes in neuroinflammation indicate the increase of the gene expression for SOD_1 in the active MS plaques [194]. Other studies point to the decrease of the activity of this enzyme with the increase of SOD_2 activity in EAE [55]. The studies of Horssen et al. [21] have shown the increase of the total activity of SOD in acute MS attacks, which is supported by the results of the recent studies on SOD activity in plasma [194]. Taking into account the existence of oxidative and nitrosative stress in the CNS [194], the reduction of SOD activity in neuroinflammation could be a part of the reduction of the total antioxidative defense, which is suggested by the results of similar studies [25, 27, 111]. The reduction of SOD activity opens up the possibility for further evolution of oxidative damages inside the CNS by the previously described mechanisms [61]. This is the explanation for the highly important negative correlation between the activity of this enzyme and the severity of the clinical picture and the radiological finding of patients with acute attacks of neuroinflammation [103].

Some earlier studies point to the increase of SOD activity in CSF in acute MS attacks [195], contrary to the results which suggest the decline of SOD activity in these patients [104]. It is possible that ROS, directly or by means of inflammatory mediators, achieve the effect on the gene expression of this enzyme [28], wherein the suppressor effect of ROS on SOD expression is potentiated over time [27]. The increase of SOD activity in erythrocytes during inflammatory processes has also been shown [123, 196]. SOD increase occurs as a consequence of adaptive compensatory reactions on prooxidative processes [21] and indicates the preservation of antioxidative potential, while a smaller increase of the activity or its absence could be a consequence of the inactivation of this enzyme by the prolonged oxidative stress which is a characteristic of MS patients even in the absence of the acute disease attacks [83]. There are studies [123] which find a correlation between SOD activity in erythrocytes and the severity of clinical picture. On the other hand, there are results which deny this type of correlation [197], although these results also suggest that the decline of SOD activity is in a negative correlation with the disease duration. Results of some studies also suggest a strong direct correlation between the decline of both total and cell antioxidative potential and the time during which the organism is exposed to prooxidative effects [122]. This effect is potentiated with the increase of patients' age [24]. It has been shown that antioxidative potential in a dose- and time-dependent form increases the antioxidative capacity of erythrocytes, thus increasing SOD activity, which prevents the occurrence of various degenerative diseases [198]. This is supported by the results of an experimental study which has shown that SOD activity increases and the clinical

presentation of neuroinflammation is mitigated after the anti-oxidative treatment [99]. It is interesting that erythrocytes, as circulating cells, are always exposed to the adverse effects of ROS, even in the absence of clinical relapses of the disease [22, 82], which makes the change of antioxidative capacity of these cells one of the important links in neuroinflammation pathogenesis [118, 119].

Modulation of Oxidative Stress in Neuroinflammation—Therapeutic Perspectives

The role of oxidative stress in the pathogenesis of neuroinflammation and demyelination is undoubtedly big. The effect of various antioxidative approaches like supplementation of oxidative enzymes in oligodendrocyte culture has been confirmed, thus achieving the protective effect, compared to the damages caused by ROS [148]. The supplementation of cystine and cysteine has shown a favorable effect on this cell line, increasing the intracellular level of GSH [153]. As shown in other experimental studies, by similar mechanisms, NAC achieves protective features in relation to the clinical manifestation of EAE [99]. The earliest supplementation by antioxidants has shown the direct but delayed favorable effect in relation to the clinical presentation of EAE, even after a short application at the beginning of the disease and a further suspension of the use of these enzymes [198]. The existence of protective features of the use of antioxidative enzymes before EAE induction was also indicated because the occurrence of the disease after a premedication with these enzymes was delayed and slow; in one percent of the cases, it did not even occur [86]. The largest number of studies indicates that the use of antioxidants affects the change of neuroinflammation course under experimental conditions, which is reflected in the reduction of the severity of clinical presentation of the disease and the total reversibility of the changes that occurred, faster achieving of remission level, and the delayed and slow course of EAE [118].

This review gives an advanced insight into the roles and the importance of oxidative stress during neuroinflammation and offers the possibility for applying antioxidative treatments in acute attacks of neuroinflammation. In this way, neuroinflammation might be controlled in early phases characterized by reversibility, at the same time delaying later phases which are accompanied with irreversible neurological disabilities.

Conflict of Interest None.

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