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Journal
Brain Research Bulletin, 55(2)

ISSN
0361-9230

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Publication Date
2001-05-01

DOI
10.1016/s0361-9230(01)00455-5

Brain Research Bulletin, Vol. 55, No. 2, pp. 125–132, 2001

0361-9230/01/$–see front matter

PII S0361-9230(01)00455-5

Mechanisms by which metals promote events connected to neurodegenerative diseases

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ABSTRACT: Although the exact causative phenomenon responsible for the onset and progression of neurodegenerative disorders is at present unresolved, there are some clues as to the mechanisms underlying these chronic diseases. This review addresses mechanisms by which endogenous or environmental factors, through interaction with redox active metals, may initiate a common cascade of events terminating in neurodegeneration. © 2001 Elsevier Science Inc.

KEY WORDS: Copper, Iron, Prion-related protein (PrP), β-amyloid, Aluminum.

INTRODUCTION

As the brain ages, distinct alterations in oxidative and inflammatory events occur that are associated with pathological lesions characteristic of neurodegenerative diseases. Copper, manganese, iron, and other trace redox-active transition metals may be involved in mediating these processes and thus may be involved in the neuropathology of disorders such as Parkinson disease (PD), Alzheimer disease (AD), and amyotrophic lateral sclerosis (ALS). Recently it has been discovered that transition metals bind to proteins involved in neurodegeneration and this association appears to preserve metal redox activity in a manner that is consistent with a pro-oxidant, free radical generating action. The binding of multivalent metals to colloidal aluminum (Al) may parallel this phenomenon. Alterations in the levels of copper- and iron-containing metalloenzymes, involved in processing partially reduced oxygen intermediates, as well as the antioxidant status of cells, may also contribute to altered redox homeostasis in neurodegenerative diseases. Nonetheless, even in familial forms of ALS, linked to mutations in superoxide dismutase, it is not clear whether an altered enzyme activity or, indirectly, a disturbance in transition metal homeostasis is involved in the disease pathogenesis. The purpose of this review is to evaluate recent publications implicating redox-active transition metal ions in promoting oxidative events. The connection between reactive oxygen moieties in promoting glial activation and the resulting pro-inflammatory cascade will be discussed. Both processes are present in the aged and diseased brain and metal-induced exacerbation of these events may contribute to the pathological lesions characteristic of neurodegeneration.

ROLE OF REACTIVE OXYGEN SPECIES IN BIOLOGICAL SYSTEMS

The side-production of superoxide during reduction of molecular oxygen by mitochondria is inevitable in all aerobic organisms. In addition, hydrogen peroxide, produced by oxidases such as monoamine oxidase, increases susceptibility to reactive oxygen of tissues enriched in these enzymes. The principal damaging intermediate of oxidative stress is the hydroxyl radical, which alters biomacromolecules present at its site of generation. In recent years, the explosion of research on the role of nitric oxide (NO) in neurotransmission has led to the recognition of "nitrosative stress". This is a form of oxidative stress that is directly linked to the reaction of superoxide with NO to give peroxynitrite or to antioxidant activity of NO. Although peroxynitrite also appears capable of hydroxyl radical-like activity, most of these highly reactive intermediates are formed by the Fenton reaction between reduced transition metals (usually iron(II) or copper(I)) and H_2O_2.

Of the various hypotheses that have been suggested for the etiology of idiopathic AD, the one receiving most attention is a role for oxidative stress. Disruption of homeostasis of redox-active metals is particularly significant since substantial evidence for increases in oxidative stress parameters exist [67,76,88,97–99,101, 113]. Whether the presence of enhanced oxidative events is the cause or the end result of the disease is not certain. Antibodies against 4-hydroxynonenal showed that neurons lacking neurofibrillary tangles also displayed hydroxynonenal (HNE)-pyrrole immunoreactivity while the age-matched controls only had background immunoreactivity [88]. Thus, in AD, oxidative stress is a preexisting condition that subsequently leads to neuronal changes associated with the disease process. Furthermore, in Down's syndrome, which leads to early onset of the pathological changes of AD, evidence of oxidative stress is found long before neuropathological changes, even at the fetal stage [22,77–79].

INFLAMMATORY EVENTS IN THE AGED AND DISEASED BRAIN: RELEVANCE TO METALS

Microglial cells become progressively active with normal aging [103] and the aged hippocampal formation contains increased reactive glia [40]. The amount of activated astrocytes are also increased in both AD and normal age-matched control brains. These reactive astrocytes are associated with both senile plaques and cerebral microvessels [39]. Furthermore, the activation of the pro-inflammatory transcription factor, nuclear factor (NF)-κB, is

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significantly correlated to an elevation in a key inflammatory enzyme COX-2, in both aging and AD temporal lobe neocortex [65].

Cytokines such as interleukin (IL)-1, IL-6, and IL-8 are primarily synthesized by activated microglia and macrophages in response to pathogens and trauma. Chronic production of these factors can result in cytotoxicity because they recruit and activate macrophages that produce high concentrations of reactive oxygen species (ROS) [43]. IL-1 and IL-6 are both elevated in the brain in AD and postischemia [23]. In an animal model of chronic inflammation, induced by infusion of lipopolysaccharide, there was astrogliosis as well as an increase in the levels of amyloid-β protein precursor (AβPP), IL-1, and tumor necrosis factor (TNF)$\propto$ mRNA levels. This was subsequently followed by hippocampal cell loss and impairment of spatial memory, all of which mirror changes seen in the AD brain [106].

REDOX ACTIVE TRANSITION METALS IN NEURODEGENERATION

Multivalent transition metals such as iron, copper, and manganese are essential in most biological reactions such as the synthesis of DNA, RNA, and proteins. They are also cofactors of numerous enzymes, particularly those involved in respiration. However, abnormal tissue accumulation of redox-active transition metals can be cytotoxic because perturbations in metal homeostasis results in an array of cellular disturbances characterized by increased free radical production. Oxidative stress, defined as the imbalance between biochemical processes leading to production of ROS and the cellular antioxidant cascade, causes molecular damage that can then lead to critical failure of biological functions and ultimately cell death. The levels of copper and iron are increased in the rims of senile plaques (SP) [64] and the presence of these redox reactive metals in both SP and neurofibrillary tangles has been shown to induce hydrogen peroxide dependent oxidation [89]. This indicates that the metals may be playing a role in modulating oxidative events, which may eventually result in neurodegeneration.

COPPER IN NEURODEGENERATION

Copper has a functional role in many enzymes that require oxidation-reduction reactions. For example, the metal is found in the catalytic site of cytochrome c oxidase of the mitochondrial electron transport chain and Cu-Zn superoxide dismutase (SOD). The entry of Cu to the brain is mainly mediated by ceruloplasmin (CP) [61]. This copper binding protein is also involved in the acute phase of inflammation and plays a role in protecting cells against oxidative stress [6]. CP is considered the major Fe(II)-oxidizing enzyme in the central nervous system (CNS), and an inherited metabolic disorder called aceruloplasminemia is associated with impairment in iron homeostasis and consequent neurodegeneration [50]. While CP is increased in brain tissue and cerebrospinal fluid in AD, PD, and Huntington's disease [63], neuronal levels of CP remain unchanged [28]. Thus, while increased CP may indicate a compensatory response to increased oxidative stress in AD, its failure to do so in neurons may play an important role in metal-catalyzed damage. In fact, studies directed at clarifying the relationship between oxidative stress and tissue metal ion levels indicate that the ratio of copper to zinc and the levels of CP are significantly higher with increasing age, and higher yet in cases with neurodegeneration [73]. Redox-inert zinc may serve as an antioxidant by preventing binding of pro-oxidant copper at tissue sites [38].

Iron in Neurodegeneration

Free iron, more than any other transition metal, has been implicated in redox transitions and consequential generation of oxygen free radicals. The potential of iron to cause an increase in oxidative events leading to cellular damage is controlled by a series of iron-binding proteins. Lactoferrin, which has been shown to protect against severe inflammation, is increased in the brain of patients with neurodegenerative diseases [44]. The iron regulatory proteins (IRP-1 and IRP-2), which control other Fe-binding proteins and thus the regulation of cellular iron metabolism, also play a role in decreasing the ROS generating capacity of Fe [60]. IRP-1, but not IRP-2, is rapidly activated by extracellular H_2O_2, establishing a regulatory connection between the control of iron metabolism and response to oxidative stress. Whereas IRP-1 was found to be present in similar levels in both AD and control brain tissue, IRP-2 co-localized with redox-active iron in neurofibrillary tangles (NFT), SP neurites, and neuropil threads [102]. These results suggest that alterations in IRP-2 may be directly linked to impaired iron homeostasis in AD. We have found a marked association of redox-active iron with both NFT and SP in AD [100].

Microglia are the major sites of ferritin bound iron and are thought to be partly responsible for oxidative damage in PD and other neurodegenerative disorders. Abnormally high levels of iron as well as oxidative stress have been demonstrated in a number of neurodegenerative disorders including AD and those characterized by nigral degeneration such as PD, multiple system atrophy, and progressive supranuclear palsy. Microglia stimulated *in vivo* with phorbol ester show increased lipid peroxidation resulting from a superoxide-dependent release of iron from ferritin [112]. In addition, the interplay between oxidative stress and control of iron metabolism in the brain is exemplified by the finding of abnormal iron deposition associated with lipid peroxidation in a transgenic mouse model (expressing IL-6 in astrocytes) of a blood—brain barrier defect associated with progressive neurodegeneration [29].

Iron-Mediated Oxidative Stress and PD

Although a mutation in the α-synuclein gene in certain cases of familial Parkinsonism has been identified, the etiology of the vast majority of cases remains unknown. Nonetheless, several biochemical abnormalities in PD have been identified, including a mitochondrial complex I deficiency, oxidative stress, and excess iron. Fe accumulates in substantia nigra astrocytes of old rats [91,92] and correlating to this is an increase in the Fe(III)/Fe(II) ratio and a decrease in glutathione (GSH) [82]. One explanation is that mitochondrial sequestration of redox-active iron in aging nigral astroglia may be a factor predisposing the senescent nervous system to Parkinsonism and other neurodegenerative disorders. In fact, a persistent condition of oxidative stress, associated with perturbed intracellular redox equilibrium, is recognized as a pathogenetic factor underlying neurodegeneration. Moreover, there is circumstantial evidence that the intracellular redox imbalance results in aberrant oxidation of dopamine to 6-hydroxydopamine, which in turn can undergo autoxidation to the corresponding quinone concomitant with generation of superoxide. This reaction, either by itself, or as amplified by redox cycling of this quinone may lead to further generation of ROS at the expense of cellular reductants. This can explain the ultimate demise of these neurons. Studies designed to clarify the mechanism of dopamine oxidation *in vitro* have demonstrated 6-hydroxydopamine conversion in the presence of Fe(II) and either H_2O_2 or alkyl peroxides [80].

THE ROLE OF PROTEIN-METAL BINDING IN NEURODEGENERATION

The misfolding of a normal constitutively expressed protein may lead to formation of protease-resistant neurofibrillary tangles. Aggregated prion-related protein (PrP) and the amyloid-β peptides are two such cases in which the irreversible formation of beta sheeted fibrils lead to microglial activation [7,94].

Prion Protein

PrP is a transmembrane glycoprotein that is constitutively expressed in both glial and neuronal cells. Although its function is unknown, the protein incorporates copper and has SOD activity [14–16,19]. The prion protein (PrPc) binds copper at its N-terminal region and PrPc-deficient mice are more prone to copper toxicity [18]. Thus, it may play a role in protecting cells from oxidative damage. The misfolding and consequent aggregation of the protein is generally accepted to be responsible for spongiform encephalopathies (prion diseases), such as the human Gerstmann-Sträussler-Scheinker's syndrome and Creutzfeldt-Jakob disease. These are characterized by the extracellular deposition of the pathological form of the PrP protein and in some cases, the co-existence of amyloid plaques, gliosis, vacuole formation, and neuronal cell death [7,20,59]. These changes parallel the pathological alterations in the brain of AD patients.

Oxidative stress is a common factor in both the aged brain and neurodegeneration and this partially may be due to the increased reactive gliosis that follows both conditions [49,85,86,103]. The prion glycoprotein, expressed on microglial cells, augments activation of these cells [17]. Microglia in turn produce ROS in response to PrP peptide (106–126) and this fragment is toxic to neuronal cell cultures only in the presence of activated glial cells [14]. *In vivo*, the brain of mice infected with scrapie showed astrogliosis and microglial activation early in the course of the disease, followed by neuronal loss [7]. This sequence of events suggests that microglia associated inflammatory events may be contributing to the cell loss.

This view is further strengthened by a recent study demonstrating that scrapie-infected mice brains show an increase in mitochondrial ROS production as well as an enhancement of NF-κB activation followed by elevated levels of IL-1α, IL-1 β, TNF-α, IL-6, and inducible NO synthase [59]. Neuronal vacuolation was present in the cortex, hippocampus and especially the thalamus and this was co-localized with NF-κB activity. Thus it appears that glial activation and consequent cytokine and ROS production may be the factors responsible for neuronal loss.

Amyloid-β Protein

The AβPP is postulated to have neurotropic properties [58,68, 72,96]. The role of the protein in protecting neurons is supported by studies that show that AβPP is upregulated during stressful conditions. The synthesis of AβPP in astrocytes increases after treatment with IL-1 [86] and transient ischemic changes modulate the expression of AβPP mRNA in rat cerebral cortex [58]. Amyloid-β is cleaved from AβPP and cultured cells derived from the CNS constitutively produce Aβ. The soluble forms of the protein are found in both normal and AD cerebrospinal fluid [32].

In many circumstances Aβ appears to act in a cytokine-like manner and promote inflammatory events. For example, Aβ and interferon-γ, as well as IL-1β, activate microglia [27,47,70,90]. These reactive glial cells not only increase NO production [1,54], but they also activate complement [37,84,104]. Aβ has also been shown to exacerbates oxidative events in cells [8,93,101]. In a recent study, it was demonstrated that Aβ generated hydroxyl radical formation was mediated by the reduction of Fe and Cu [52]. Parallel to the function of interleukines, the subsequent secretion of Aβ may be an integral part of an attempted innate immune response of the CNS against pathological conditions. If the disturbance is not resolved, the chronic production of these potentially harmful substances can then lead to neurodegeneration.

Copper has been shown to bind to AβPP which then reduces the metal from Cu (II) to the ROS generating Cu (I) [75]. This is analogous to the binding of copper to the Prp protein [26]. The addition of antioxidants such as SOD and catalase did not inhibit this ability of the AβPP protein to bind and reduce copper [74]. Copper has been shown to cause aggregation of Aβ and this increases the toxicity of the protein in neuronal cell cultures [53]. Different fragments of the amyloid-β peptide also reduce copper and generate hydrogen peroxide and it was observed that Aβ1-42 is more toxic than Aβ1-40. This was associated with the copper reduction capability of the peptides [52]. The generation of hydrogen peroxide occurred at catalytic amounts of Cu and thus these reactions may be occurring *in vivo*. NF-κB is activated by hydrogen peroxide and copper present as a particulate in air pollution can activate this pro-inflammatory transcription factor [57].

Recent studies suggest that the aggregatory effect of metals depends critically on pH. Cu(II) induced aggregation of Aβ_{1-40} when the pH was lowered from 7.4 to 6.8. This phenomenon was not common to other metals tested [3]. A mildly acidic environment, together with increased Zn(II) and Cu(II), are common features of inflammation and this could explain the rapid deposition of Aβ following head injury as well as inflammation associated with increased oxidative damage due to microglial-derived peroxynitrite.

Both Aβ and aluminum sulfate are able to stabilize ferrous iron, which is the active form of the metal involved in the promotion of hydroxyl radical formation by the Fenton reaction [110]. In isolated systems Al potentiates iron promoted oxidative stress [10] and in the presence of the metal, iron can enhance ROS formation in protein-free liposomes [11]. Aluminum seems able to promote the pro-oxidant potential of iron rather than possessing any intrinsic ROS-generating capacity. It is possible that parallel to PrP and Aβ, colloidal Al may bind Fe and thus modulate the generation of ROS.

The Potential Role of Colloidal Aluminum in Neurodegeneration

Aluminum exposure and its relevance to neurodegeneration has been the subject of much controversy in the last few decades. In 1976, Alfrey implicated Al as the agent responsible for the outbreak of a dialysis encephalopathy syndrome [4] and in a later study it was demonstrated that the symptoms completely disappear after cessation of oral aluminum intake [87]. This Al-induced encephalopathy has also been reported in patients who have undergone bladder irrigation with 1% alum [81]. Residing in districts with high Al concentrations in the municipal drinking water has been linked to an increased risk of developing AD [69]. However, although it has been demonstrated that Al levels are increased in the brains of AD patients some studies repudiate this and thus the issue remains controversial [9,36,109].

Aluminum has been shown to exacerbate ROS formation *in vivo* and *in vitro*. Intraperitoneal injection of aluminum gluconate increased the rate of ROS formation in cortical tissue [12] and the brain of rats treated with aluminum lactate for 4 weeks showed an increase in lipid peroxidation and a significant decrease in antioxidants [55]. Al increased ROS formation, accompanied with elevated mitochondrial activity and glutathione depletion, in glial but not neuronal cell lines [24]. Because Al salts, complexed to strong acids such as sulfate and chloride, have a strong tendency to

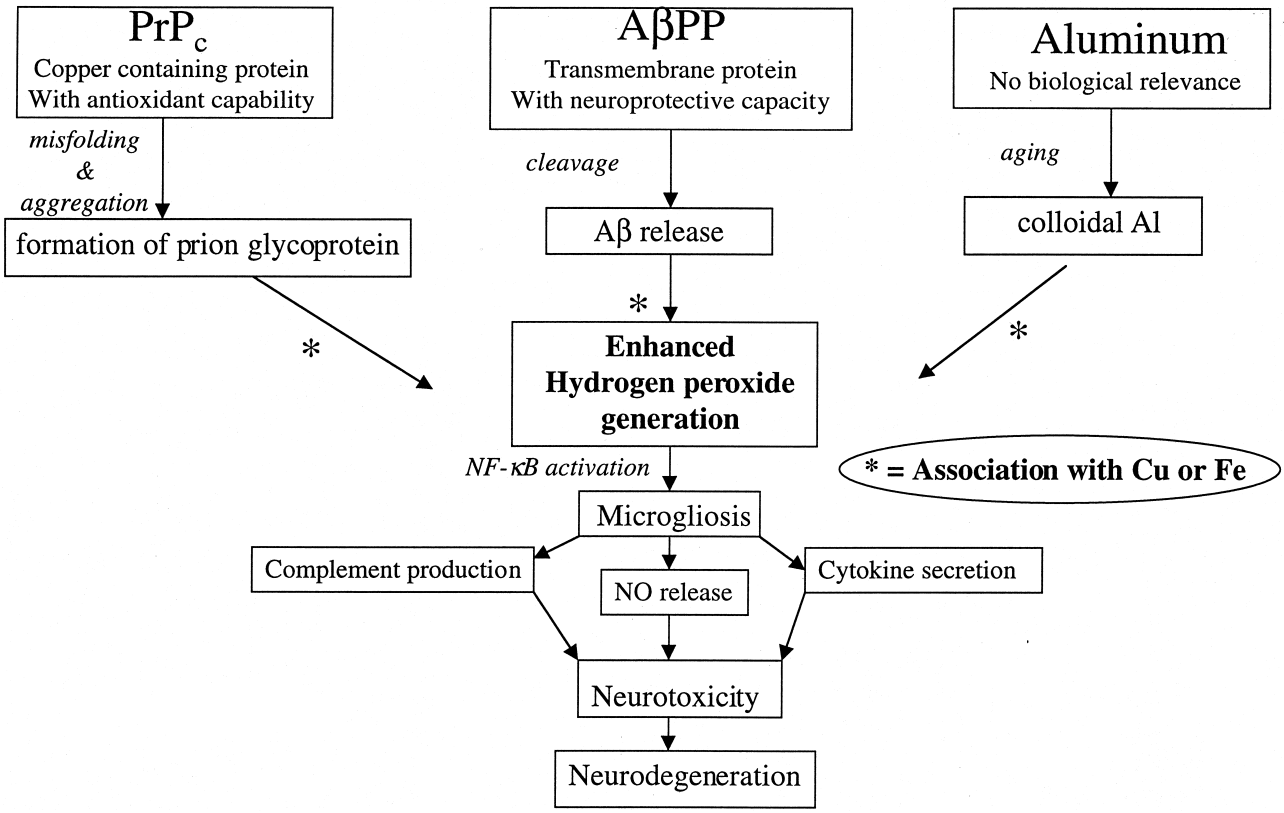

FIG. 1. Transition metal/particle surface complexes may initiate a common chronic inflammatory pathway culminating in neurodegeneration.

form colloidal particles as they age [33], it is possible that the aluminum sulfate-induced increase in ROS generation is due to a glial response to the extracellular aluminum particles.

Several studies demonstrate that aluminum can cause a systemic inflammatory response. Low doses of aluminum, present in parenteral nutrition formula, produced marked portal inflammation [42] and rats exposed to oral doses of Al show an increase in plasma α1 globulins [30]. Aluminum sensitization can develop in some children vaccinated for diphtheria, tetanus, and pertussis and Al-induced inflammatory nodules are formed in adults revaccinated for hepatitis B because the vaccines contain aluminum hydroxide as an adjuvant [35]. Aluminum, upon entry, may also initiate an inflammatory cascade in the brain. Chronic Al lactate treatment of rabbits increases glial fibrillary acidic protein concentrations in the frontal cortex [111] and the metal also increases NF-κB activation in human glioblastoma cells [25]. This transcription factor is known to bind to and promote the production of nitric oxide synthase [5] and aluminum can induce the production of NO by microglial cells when it is in an insoluble form [45].

ANTIOXIDANT ENZYMES AND PROTEINS INVOLVED IN TRANSITION METAL HOMEOSTASIS

The development of transgenic mouse models has permitted a range of studies that critically evaluate the extent to which selected biological processes affect cell viability. MnSOD "knock-out" mice, suffering a 50% drop in mitochondrial SOD activity but no reduction of CuZnSOD or GSH peroxidase activity, were found to exhibit increased oxidative damage to mitochondria [108]. In contrast, no damage to cytosolic proteins or to nuclear DNA was observed. Analysis of homozygote "knock-outs" showed mitochondrial degeneration that could only be followed for the 2 weeks that these mice were alive [71]. These results suggest that decreases in MnSOD activity can explain increased oxidative damage in mitochondria and alterations in the essential function of this organelle.

Overexpression of human CuZnSOD in mice, resulting in a 10-fold higher level in both myocytes and endothelial cells, was able to quench a burst of superoxide (electron probe resonance [EPR] detection) and reduce functional damage following 30 min global ischemia [105]. These results suggest that superoxide is an important factor in protecting against postischemic injury. However, it is surprising that CuZnSOD "knock-out" mice show little if any neurodegenerative phenotype [21]. Nonetheless, it is apparent that decreases in CuZnSOD activity can lead to a perturbation of cellular antioxidant defense mechanisms and promote a prooxidant situation.

The CuZnSOD gene is associated with AD neuropathology, and levels of both MnSOD mRNA and CuZnSOD were found to increase in AD, whereas the total antioxidant status was decreased [66]. Similarly, the activity of CuZnSOD in erythrocytes and the lymphocyte mRNA level of MnSOD were significantly increased in AD patients while total plasma antioxidant capacity was diminished [41]. In the brain tissue of AD patients, the activity of catalase and SOD is decreased, followed by an increase in lipid peroxidation [67]. These changes in antioxidant defense mechanisms may be responsible for the increased levels of oxidatively damaged RNA and proteins in AD brains [76].

In the scrapie-infected hamster brain, there is an increase in the

activity of glutathione peroxidase and reductase while the activity of mitochondrial manganese SOD is decreased [31]. This change in mitochondrial antioxidant defense may be responsible for the low level of ATPase activity and the high level of lipid peroxidation found in the cerebral mitochondria of infected animals. In cell culture, prion protein (106–126) induces heme oxygenase-1 (HO-1) in astroglial cells but not neuronal cells [83]. Thus, prion proteins modulate antioxidant status of cells and this may, in part, play a role in the eventual neurodegeneration observed in prion-infected brains.

CuZnSOD Mutations and Familial ALS

An important breakthrough in our understanding of ALS comes from the finding that many of the familial cases (FALS) are associated with mutations in the CuZnSOD gene. The protein products of these mutations retain nearly identical SOD activity, but take on altered properties linked to oxidative stress, possibly involving a gain-of-function peroxidase activity [107]. Transgenic mice overproducing a human FALS CuZnSOD mutant display increases in protein carbonyls suggestive of increased hydroxyl radical production or lipoxidation-derived radicals [2]. Using *in vivo* microdialysis, increased hydroxyl radical production in the striatum was seen for mice overexpressing the mutant enzyme relative to mice overexpressing the wild type human enzyme [13]. The hypothesis that mutant SOD-induced neurodegeneration is associated with disturbances in neuronal free radical homeostasis is further supported by observations made on several neuronal cell cultures expressing the mutant SOD [46]. However, the mechanism underlying the link between the SOD mutations and oxidative stress indicators appears not to be simply increased production of hydroxyl radicals, since no increases in HO• adducts are seen *in vitro* for the Gly93Ala and Ala4Val mutants relative to wild-type enzyme [95].

Recent studies have shown that the mutant and wild-type SODs differ neither in the rates of superoxide dismutation, nor in another enzyme diagnostic, namely H_2O_2-mediated inactivation [48,62]. Structural analysis of the mutant enzymes revealed that in some cases there were alterations such as subunit asymmetry. This suggested aberrant copper-mediated redox chemistry stemming from decreases in the tight folding and thus a more open "active site" [34,51]. Thus, the gain-of-function activity may reflect a "rechanneling" of the enzyme to oxidize biomolecules that normally would never gain access to the SOD oxidative half-reaction. Alternatively, the mutant SOD may possess weakened affinities for zinc or copper leading to a fraction of enzyme with abnormal activity [95] or oxidative reactions associated with leakage of copper [48]. For the predominant, sporadic form of ALS, an imbalance in trace metal ions, possibly tied to increased oxidative stress, has been considered for some time. Recent studies provide evidence for decreases in copper in the cerebrospinal fluid and serum as well as increases in manganese in serum of diseased individuals compared to age-matched control [56].

CONCLUSION

Over the past few years, there has been an increasing awareness of the seminal role that redox-active transition metals play in a variety of neurodegenerative diseases. The physico-chemical properties of aggregated prion proteins, fibrillar βA, and colloidal aluminum are very compatible with the promotion of oxidative stress by providing a complexing surface for redox-active metals and thus allowing activation of pro-oxidant events. These properties are also appropriate for inducing ineffectual glial responses. Failure to disperse these xenobiotic inclusions within the CNS can lead to chronic inflammatory responses and increased ROS production that ultimately involve neurons and impair their function (Fig. 1). Presently, the stage is set to critically examine the importance of therapeutic modalities such as antioxidants, chelating agents and non-steroidal anti-inflammatory drugs in the treatment of neurodegenerative disorders.

ACKNOWLEDGEMENTS

The work conducted in the laboratory of the authors was supported by grants from the National Institute of Health and the Alzheimer's Association.

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