Elucidation of Endemic Neurodegenerative Diseases – a Commentary

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Recent investigations of scrapie, Creutzfeldt-Jakob disease (CJD), and chronic wasting disease (CWD) clusters in Iceland, Slovakia and Colorado, respectively, have indicated that the soil in these regions is low in copper and higher in manganese, and it has been well-known that patients of ALS or Parkinson's disease were collectively found in the New Guinea and Papua islands, where the subterranean water (drinking water) contains much Al^{3+} and Mn^{2+} ions. Above facts suggest that these neurodegenerative diseases are closely related with the function of a metal ion.

We have investigated the chemical functions of the metal ions in detail and established the unique mechanism of the oxygen activation by the transition metal ions such as iron and copper, and pointed out the notable difference in the mechanism among iron, aluminum and manganese ions. Based on these results, it has become apparent that the incorporation of Al(III) or Mn(II) in the cells induces the "iron-overload syndrome", which is mainly due to the difference in an oxygen activation mechanism between the iron ion and Al(III) or the Mn(II) ion. This syndrome highly promotes formation of hydrogen peroxide, and hydrogen peroxide thus produced can be a main factor to cause serious damages to DNA and proteins (*oxidative stress*), yielding a copper(II)- or manganese(II)-peptide complex and its peroxide adduct, which are the serious agents to induce the structural changes from the normal prion protein (PrP^C) to abnormal disease-causing isoforms, PrP^{Sc}, or the formation of PrP 27–30 (abnormal cleavage at site 90 of the prion protein).

It seems reasonable to consider that the essential origin for the transmissible spongiform encephalopathies (TSEs) should be the incorporation and accumulation of Al(III) and Mn(II) ions in the cells, and the sudden and explosive increase of scrapie and bovine spongiform encephalopathy (BSE) in the last decade may be partially due to "acid rain", because the acid rain makes Al(III) and Mn(II) ions soluble in the subterranean aquifers.

Key words: Endemic Neurodegenerative Diseases, Aluminum and Manganese Ions, Iron-Overload

Introduction

Transmissible spongiform encephalopathies, or TSEs, are a family of neurodegenerative diseases found in both humans and animals (Prusiner, 1998; Checler and Vincent, 2002; Collinge, 2001; Vincent *et al.*, 2000). The oldest known member of this family is scrapie in sheep and the most famous member is bovine spongiform encephalopathy (BSE), or "Mad Cow Disease". Recent investigations of scrapie, Creutzfeldt-Jakob disease (CJD), and chronic wasting disease (CWD) clusters in Iceland, Slovakia and Colorado, respectively, have indicated that the soil in these regions is low in copper and higher in manganese, and it has been well-known that patients of ALS or Parkinson's disease were collectively found in the New Guinea and Papua islands, and thus the above neurodegenerative diseases are sometimes called a kind of the endemic diseases.

Prusiner has been one of the leaders of attempts to determine the infection source for TSEs, and which he claims is an abnormal form (PrP^{Sc}) of the host normal prion protein (PrP^C). It has been known that scrapie or BSE is associated with accumulation of PrP^{Sc}, and in many medical points of view it is similar to other neurodegenerative diseases such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS) (Checler and Vincent, 2002).

The normal prion protein (PrP^C) is a highly conserved cell surface glycoprotein expressed by a broad range of cells and in particular by neuronal cells (Checler and Vincent, 2002; Collinge, 2001). In TSEs, this molecule is converted into a conformationally modified protease-resistant isoform called PrP^{Sc} (Prusiner, 1998; Checler and Vincent, 2002; Collinge, 2001), or the formation of PrP27-30 has occurred, the latter is caused by the abnormal

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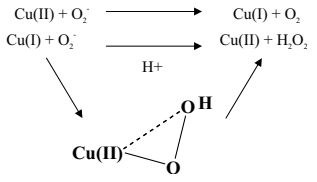
cleavage at about site 90 of isoform PrP^{Sc} (Collinge, 2001; McMahon *et al.*, 2001). Although advances have been made in understanding prion diseases, the function of PrP^{C} remains elusive. Studies based on structural homology have revealed the limited information concerning the function of the protein. However, it was shown that the octapeptide repeat region of the molecule binds Cu ion, and it has been proposed that PrP^{C} may play a role in the oxidative stress of the cell through a regulation of the copper transport and/or through a modification of Cu/Zn superoxide dismutase activity (Brown and Besinger, 1998; Brown *et al.*, 2001), which may be consistent with the increasing data that oxidative stress plays a role in other neurodegenerative diseases, such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS) (Simonian and Coyle, 1996; Sherman and Goldberg, 2001).

ALS and copper(II)-hydroperoxide adduct

ALS, also called motor neuron disease, or Lou Gehrig's disease, is a progressive disorder that is usually fatal within 5 years of onset of symptoms (Brown, 1995) The paralysis is due to degeneration of large motor neurons of the brain and spinal cord; the underlying cause of the degeneration is not clear at present. About 10% of ALS cases are familial (FALS). SOD1, the gene encoding the cytosolic antioxidant enzyme Cu, Zn, superoxide dismutase (SOD), was studied as a FALS candidate because of (1) its proximity to a FALS locus mapped to chromosome 21q22.1 in a subset of FALS, (2) decreased SOD activity in the cerebrospinal fluid of some ALS patients, (3) the important function of SOD in free radical homeostasis, and (4) the role of free radical in neurodegeneration. It has been indicated that single-site mutants in the Cu,Zn-SOD gene occur in patients with FALS; complete screening of the SOD1 coding region revealed that the mutation Ala4 to Val in exon 1 was the most frequent one. The crystal structure of human SOD, along with two other SOD structures, established that all 12 observed FALS mutant sites alter conserved interactions critical to the β-barrel fold and dimer contact, rather than catalysis. Thus, the defective SOD is linked to motor neuron death and carries implications for understanding and possible treatment of FALS, but the chemical relation among the structure of the mutation, the decreased SOD function, and appearance of "gain-of-function" is not clear at present (Deng *et al.*, 1993; Pazos *et al.*, 1993; Rabizadeh *et al.*, 1995; Goto *et al.*, 2000; Estevez *et al.*, 1999).

We have pointed out (Nishida and Nishino, 1999) that the chemical effects by change of the protein structure around the copper(II) ion in SOD is very important to understand the "gain-of-function" of mutant SOD. We proposed that that dismutation of superoxide ion proceeds through formation of a copper(II)-peroxide adduct shown in Scheme I (Nishida *et al.*, 1994): the peroxide ion formed in the above reaction removes from the enzyme quickly, and is decomposed by calatase or glutathione peroxidase into oxygen and water.

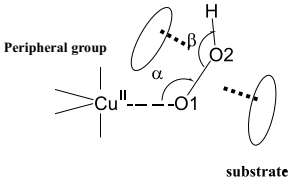


Scheme I.

It seems quite likely that the release of this peroxide ion from the copper(II) ion is prevented by the organic groups around the peroxide ion in the mutant SOD of ALS patients (and also maybe in the mutant PrP^{C} protein). The studies on the model compounds have revealed that the life-time, stability and reactivity of a copper(II)-peroxide adduct are highly dependent on the angle, β (see the Scheme II below), and *this angle is determined through the chemical interactions with the peripheral groups and the substrate near the peroxide ion* (Nishino *et al.*, 1999; Nishino *et al.*, 2000; Nishino *et al.*, 2001b; Nishino and Nishida, 2001); some cases the peroxide adduct acts as an electrophile, leading to C-N bond cleavage of the peptide bond, function (A) (Nishino *et al.*, 2000), and in another cases it acts as a nucleophile, leading to conformational change of the peptide, but without cleavage, function (B), (Nishino *et al*, 2001b) and function (C), where the peroxide adduct gives an oxygenated substrate without the decomposition of the protein (Nishino and Nishida, 2001).

In the wild-type SOD, release of the peroxide ion should be easy, because there is no chemical group to interact with the hydroperoxide ion of

the intermediate species in Scheme I. The calculated results based on Density-Functional Theory (DFT) (Nishino *et al.*, 2001a; Nishida and Nishino, 2001) are consistent with the above discussion, *i.e.*, the reactivity of a copper(II)-hydroperoxo species is highly dependent on the angle β (= < O-O-H) in the above figure, and the angle β is determined by the interaction of a copper(II)-OOH, substrate (in this case the peptide group) and the peripheral groups. These results obtained above clearly explain the observed facts, *i.e.*, origin for the "gain-of-function" of the mutant SOD as described above, (Deng *et al.*, 1993; Pazos *et al.*, 1993; Rabizadeh *et al.*, 1995; Goto *et al.*, 2000; Estevez *et al.*, 1999) and also the results reported by Requena *et al.* (2001) and McMahon *et al.* (2001).



Scheme II.

Since it has become apparent that prion protein, PrP^C exhibits high affinity for copper(II) coordination, the discussion as developed for mutant SOD should be applied to PrP^C; *i.e.*, conformational change and abnormal cleavage observed in the normal PrP^C may be attributed to the chemical function of a copper(II)-peroxide adduct formed in the surface of the cell. Eexcess hydrogen peroxide in cells is already known as a usual situation (Behl *et al.*, 1994; Nishida, 1999), and this should be mainly attributed to the "iron-overload syndrome" as described later. Thus we can postulate that the most fundamental risk factors for the induction of BSE, *i.e.* formation of PrP^{Sc} and PrP 27–30 (cleavage at site 90 of the PrP^{Sc} protein) (Collinge, 2001), should be due to the formation of a copper(II)-peroxide adduct on the cell, and conversion from PrP^C to PrP^{Sc}, is due to functions (B) and (C) as described above, and formation of the PrP (27–30), to function (A) in the PrP^{Sc} protein. *These are all attributed to a copper(II)-hydroperoxide species whose functions are greatly enhanced through interaction with the chemical groups in the altered conformational environment around the copper(II) ion of the mutant PrP^C protein, and also in PrP^{Sc}* (Collinge, 2001).

The hamster prion strain Sc237 can convert healthy mouse prion protein into the aberrant form (Hill *et al.*, 2000). So it is quite likely that PrP^{Sc}, the infected prion protein can jump from one species to another. Thus it seems quite possible that BSE may be transmitted to human from cattle. Based on this consideration the sudden increase of scrapie and BSE in the last decade may lead to conclusion that *a new risk factor has appeared recently, and which is undoubtedly an Al(III) ion and a Mn(II) ion* (Nishida, 1999; Brown *et al.*, 2000).

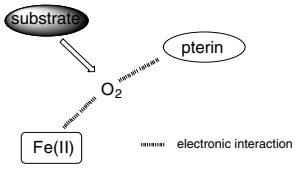
Al(III) ion and origin of its neurotoxicity

It is generally recognized that aluminum (Al) is unquestionably neurotoxic in both experimental animals and certain human diseases (Savory *et al.*, 1996; He and Strong, 2000). Minute quantities injected intracerebrally into rabbits will induce severe neurological symptoms and neuropathological features of neurodegeneration. There are many other examples of Al-induced neurotoxicity, however, the question as to whether Al presents a health hazard to humans as a contributing factor to Alzheimer's disease is still subject of debate. Several lines of evidences are presented that have formed the basis of the debate concerning a possible pathogenic role for Al in Alzheimer's disease. Important evidence for an Al-Alzheimer's causal relationship is the observation by laser microprobe mass analysis (LMMS) of the presence of Al in neurofibrillary tangles. There is another evidence that exposure to Al from drinking water might result in cognitive impairment and increased incidence of Alzheimer's disease. However, these epidemiological studies have inherent problems that must be scrutinized to determine whether an association really does exist.

Several years ago we pointed out that the establishment of a chemical mechanism on the Al(III)-induced neurodegeneration is necessary in order to prevent the humans from the Al-induced neurodegenraito, (Nishida and Ito, 1995a; Nishida, 1999) such as Alzheimer's, amyotrophic lateral sclerosis, etc. As it has been shown that transferrin, one of the major iron transport proteins in vertebrates, binds specifically Al(III) ion with a high affinity (Nishida and Ito, 1995a; Nishida,

2001) it seems quite likely that the iron ion bound to phenylalanine or tyrosine hydroxylase (THO) in brain is replaced by Al(III) ion (Nishida and Ito, 1995a; Nishida, 2001). The enzymes phenylalanine hydroxylase or THO play an important role to synthesize the dopamine; it is well known that the deficiency of dopamine is an important origin for Parkinson's disease.

Recently we proposed a new mechanism for THO (Nishida, 2001); in our mechanism the importance of complex formation among the enzyme, oxygen and pterin was pointed out; *i.e.*, *the oxygen in the complex is activated through electronic interaction with the pterin and Fe(II) ion, to catalyze the oxygenation of the benzene rings of tyrosine or phenylalanine* (see Scheme III). The activation of oxygen (oxygen in Scheme III behaves as a single oxygen ($^1\Delta_g$)) is attained through the electronic interaction between an Fe(II) ion, where the both the unpaired electrons of Fe(II) and oxygen play an important role for the complex formation between them (Nishida, 2001). It is clear that the Al(III) ion has no unpaired d-electron, and this should be a main origin for neurotoxicity by Al(III) ion in brain, because the replacement of the iron ion in the enzymes (THO or phenylalanine hydroxylase) by Al(III) ion will lead to the deficiency of dopamine in the brain , since the enzymes cannot catalyze the oxygenation of phenylalanine or tyrosine. Our conclusion has been supported by the fact that drastic improvement was observed in the symptoms when the ironized substances were administered to the Parkinson's disease patients (Imagawa *et al.*, 1992).



Scheme III.

Hydrogen peroxide formation due to "iron-overload syndrome"

Since dopamine is deficient in the brain under the above condition, the brain will order the transferrin to transport the iron ion to the enzyme, but the transported metal ions including Fe(III) and Al(III) will be discarded to the tissue, because the enzyme is loaded with the metal ion, Al(III). This condition, when iron (III) ions are rich in the tissue, is called, "iron-overload syndrome" (Gerlach *et al.*, 1994; McCord 1996; Double *et al.*, 1998; Nishida and Ito, 1995b) and these iron ions are present with the polymeric structures as exemplified for ferritin. It has been shown that these *polymeric iron ions promote the formation of hydrogen peroxide in the presence of reducing agents* (Nishida *et al.*, 1992). For example, as illustrated in Fig. 1, four ESR signals characteristic for the DMPO-OH appear immediately after the addition of DMPO (a common ESR spin-trapping reagent for OH-radicals) to the solution containing a binuclear iron(III) complex, $Fe_2(HPTP)(OH)(NO_3)^{4+}$. But, this does not mean that there is a OH-radical in the solution, because no such signal was detected when the monomeric complex, $Fe(edta)^-$ was added to the solution under the same experimental conditions (trace B in Figure 1). This was elucidated as follows; *i.e.*, *the DMPO (which in this case acts as an electron donor) promotes the electronic interaction between the iron(III) complex and oxygen, as illustrated in Scheme-IV, to produce hydrogen peroxide.* In this scheme, the interaction between the unpaired electrons of Fe(III) ion and oxygen is important, which is supported by the fact that the binuclear Al(III) complex with H(HPTP), $[Al_2(HPTP)(OH)Cl_2]^{2+}$, cannot produce hydrogen peroxide under the same experimental conditions, and most likely DMPO plays both roles of pterin and substrate in Scheme III.

In many reports it has been experimentally confirmed that iron species of the polymeric form react with hydrogen peroxide to activate it, leading to the degradation and modification of proteins and DNA: (the so-called "*oxidative stress*") (Nishida, 1999). This should be a main origin for the appearance of the mutant SOD, and also mutant PrP^C in the cells, and the latter event leads to the facile formation of PrP^{Sc} as described in the previous section (Ellis and Pinheiro, 2002). The unique reactivity towards oxygen observed for dimeric iron(III) compounds has also been found for the dimeric copper(II)-species (Nishida *et al.*, 1985), and thus it seems most likely that the neural cell death induced by the polymeric or aggregated amyloid (Zou *et al.*, 2002) or prion protein should be due to the "*oxida-*

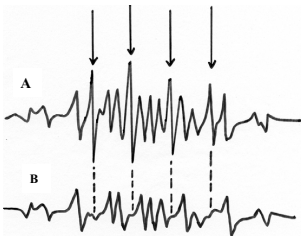
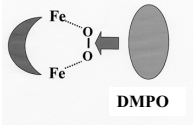


Fig. 1. ESR spectra of the solution containing DMPO and iron(III) complex
(A): DMPO + $Fe_2(HPTP)(OH)(NO_3)^{4+}$
(B): DMPO + $Fe(edta)^-$.



Scheme IV: DMPO promotes the interaction between oxygen and binuclear iron(III) species to produce hydrogen peroxide.

tive stress" by the polymeric copper(II) species, because these proteins contain copper(II) ions.

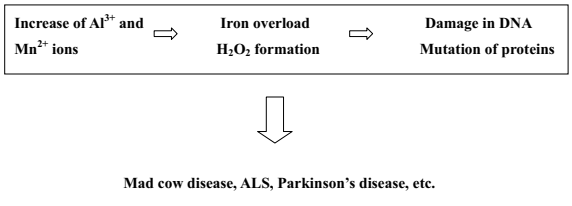
The Al(III) ion in question may originate from the dissolution of Al_2O_3 in the inner crust of the earth, which is induced by the lowering of pH of the subterranean by the "acid rain" (Peart, 2000; Kong *et al.*, 2000; Williams, 1999). The sheep eat the grass containing high concentration of Al(III), and cattle eat the feed containing ground-up carcasses of prion-infected sheep. The same discussion as described for Al(III) ion may be applied to Mn(II) ion as outlined below.

Mn(II) ion and its role in scrapie

Recent investigations of scrapie, CJD, and chronic wasting disease clusters in Iceland, Slovakia and Colorado, respectively, have indicated that the soil in these regions is low in copper and higher in manganese (Brown *et al.*, 2000). It is a controversial but intriguing possibility that imbalances in environmental cations entering the food chain may induce conditions favouring the formation of proteinase-resistant PrP^C. Brown *et al.* have shown that incorporation of manganese into PrP^C makes it proteinase-resistant and have pointed out that this is the first reliable process by which proteinase-resistant native PrP^C can be produced by cells (Brown *et al.*, 2000), but we have pointed out that a free manganese(II) ions as Mn(II) chloride used by Brown *et al.* in his experiments does not exist in cells (Nishida, 1999). Very recently we have observed that several manganese(II) chelates containing peptide groups easily bind to proteins such as SOD or transferrin etc., and that these Mn(II) chelates can activate oxygen in the presence of an aliphatic aldehyde (Togashi *et al.*, 2002). It should be noted here that the manganese(II) complex generally exhibits a behavior towards oxygen activation different from that of iron ions; *i. e.* the two-electron oxidation of Mn(II) ion is more favorable giving a stable Mn(IV) species, but in the case of the iron compounds a one-electron reaction is usual between the iron(III) and iron(II) ion, and this process is reversible (Sasaki *et al.*, 1998). The discussions described above imply that the accumulation of Mn(II) chelates in brain should promote the conformational changes of the protein, and produce the serious damages to phenyalanine hydroxylase and tyrosine hydroxylase similar to that discussed for the Al(III) ion leading to neurodegeneration in the brain.

Conclusion

The recent results described above may support that the essential origin for the transmissible spongiform encephalopathies (TSEs) can be the incorporation and accumulation of Al(III) and Mn(II) ions in the cells (Scheme V), and the sudden and explosive increase of scrapie and BSE in the last decade may be partially due to "acid rain", because the acid rain makes Al(III) and Mn(II) ions soluble in the subterranean water (Pina and Cervantes, 1996).



Scheme V.

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