

Food, Nutrition, and Neurodegeneration

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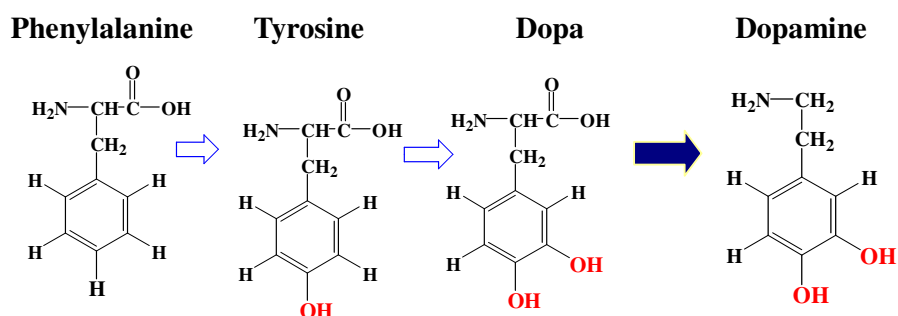
Between 1980 and roughly 1996, about 750,000 cattle infected with *BSE* (bovine spongiform encephalopathy) were slaughtered for human consumption in Great Britain, and it is now clear that BSE, also known as “*mad cow disease*” is not merely a UK phenomenon, nor is it merely an economic nuisance. The sudden and explosive increase of BSE in recent Europe may have been spread among cattle by the feeding of infected offal but the majority of cases of naturally occurring prion diseases arise *sporadically with no known cause*. Thus, ***the most important problem to be solved is to elucidate the intrinsic chemical mechanism of the prion diseases which arise sporadically.***

The sporadic neurodegenerative diseases are in general *endemic*; many years ago ALS (amyotrophic lateral sclerosis) patients were collectively found in the New Guinea and Papua islands, and its origin has been attributed to the *drinking subterranean water, which contains much Al^{3+} and Mn^{2+} ions*, and in these regions many patients of Alzheimer’s and Parkinson’s diseases were found, and increased aluminum levels were reported in the hippocampus of patients with Alzheimer’s disease. In Alzheimer’s disease specific region such as the hippocampus and the motor cortex contain elevated iron levels relative to normal, whereas the occipital cortex contains decreased levels, and **abnormalities in brain iron metabolism have been described for several neurodegenerative disorders**, including Alzheimer’s diseases, Parkinson’s disease, Huntington’s, and prion diseases. 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*, and Brown et al. observed striking elevation of manganese ion accompanied by significant reduction of copper ion bound to purified PrP in all sCJD (sCJD = *sporadic CJD*) variants. Brown et al. have reported that it loses the SOD-like activity when Cu is replaced with Mn in recombinant PrP, and also that Cu binding to PrP purified from sporadic CJD was significantly decreased while the binding of Mn and Zn was markedly increased. These results suggest that altered metal-ion occupancy of PrP plays a pivotal role in the pathogenesis of prion diseases.

In this lecture I will show the new concept on the “oxidative stress” induced by the metal ions such as copper, manganese, and iron, etc, which lead to the sporadic prion diseases and other neurodegenerative diseases such as ALS, Alzheimer’s and Parkinson’s, diseases, and you will recognize that we must pay attention to the meals and foods in our daily life in order to prevent the increases of Al^{3+} and Mn^{2+} ions in brain, which should be useful to prevent the mental diseases such as depression, schizophrenia, and violent or rough children in Japan.

Deficiency of Neurotransmitters and Neural Cell Death due to Oxidative stress

Parkinson's disease (PD) is a common neurodegenerative disorder that is clinically characterized by tremor, bradykinesia, rigidity, and loss of postural reflexes. It is generally believed that the major symptoms of PD are caused by a striatal *dopamine* (DA) deficiency, secondary to degeneration of nigrostriatal dopaminergic neurons and possibly a decreased DA-biosynthetic capacity in the surviving cells. The chemical mechanism of dopamine synthesis has been elucidated, and the result is illustrated below. Dopamine is synthesized from phenylalanine and tyrosine, one of the 20 essential amino-acids through the oxygenation reaction at the benzene ring by the enzymes, phenylalanine hydroxylase (PAH) or tyrosine hydroxylase (TH). It should be noted here that the oxygenation at the benzene ring does not occur in the air without the catalyst, *and thus it is necessary for us to know the detail chemical mechanism of the enzymes, TH or PAH, and or tryptophan hydroxylase, which catalyzes the formation of serotonin from tryptophan*; the deficiency of serotonin has been proposed to induce several mental diseases, such as *depression and schizophrenia*, etc.



TH is a *non-heme iron protein* that uses one molecule of dioxygen to hydroxylate its amino acid and tetrahydropterin substrates to hydroxy-amino acids and 4a-hydroxytetrahydropterins, respectively. The active site structure and catalytic mechanism of the aromatic amino acid hydroxylases have been investigated by kinetic and spectroscopic techniques, as well as by site-directed mutagenesis. *The iron is necessary for catalytic turnover, and thus, it is clear that iron-deficiency should lead to deficiency of neurotransmitters, such as dopamine, serotonin, etc.*

Increased brain iron (so-called non-specific iron ions) concentrations at some special regions have been described in Parkinson's disease, ***but these iron ions do not contribute to the formation of dopamine.*** The cause of nigral cell death in the Parkinson's disease remains unsolved, but many authors have pointed out the hypothesis that the cellular degeneration observed results from *oxidative stress, which should be due to the increased iron ions as described above. My new concept on oxidative stress* show that deficiency of neurotransmitters due to the abnormal iron metabolism in brain is closely related with the neural cell death, finally will lead to the pathogenesis of many neurodegenerations.

Nishida's Concept on the "Active oxygen species"

I have pointed out the importance of the electronic interaction between oxygen and the substrate in the ternary complex ESO_2 (E=oxygenases, S=substrate) in many oxygenases, and **proposed the new concept on the oxygen activation, i.e., the substrate and peripheral organic moieties around the metal ion plays an important role in activating oxygen, and determining the reaction pathway and the products in the oxygenases.** In addition to the above, I have observed **that in many cases oxygen (O_2) and hydrogen peroxide ion (O_2^{2-}) exhibits chemical reactivity similar to that of singlet oxygen ($^1\Delta_g$) in the presence of several metal ions such as iron(II), iron(III) or copper(II); in these cases, the electronic structures of triplet oxygen or peroxide molecule is changed through the interaction with a d-electron of metal ion, and this effect is greatly promoted by the peripheral organic group or substrate.** These findings are especially important to elucidate the “gain-of-function” observed for ALS patients, and also to investigate the chemical mechanism in several oxygenases, such as Lipoxygenase, *TH*, *PAH*, and *tryptophan hydroxylase*.

Al³⁺ ion in Neurodegenerative Diseases

In the iron-containing enzymes, it is clear that an unpaired d-electron plays an important role in activating O_2 . If the Fe(II) is replaced by another metal with no unpaired d-electrons such as Al^{3+} ion, it is quite likely that such enzymes cannot activate O_2 , thus giving rise the deficiency of the neurotransmitters. As shown above, ALS and Parkinson’s and Alzheimer’s patients were collectively found in the New Guinea and Papua island, and its origin has been postulated to be the drinking subterranean water, which contains much concentrations of Al^{3+} (and Mn^{2+}), and increased aluminum and manganese levels were reported in the hippocampus and the motor cortex patients with Alzheimer’s disease and in the brain of CJD patients, respectively. Thus, it seems likely that the elevated concentration of the Al^{3+} is a one of the serious origins of these neurodegenerative diseases.

Manganism ----- Mn²⁺ ion in Neurodegenerative Diseases

In many iron-containing enzymes concerning the preparation of neurotransmitters, substitution of iron with other divalent metal ions (Zn(II), **Mn(II)**, Co(II), Mg(II), and Ni(II)) results in the complete loss of enzymatic activity. These facts are clearly show that the oxidation activity by the Fe(II) ion is completely different from those of other metal ions, especially *Mn(II)*.

As a nutrient, manganese is an essential component of several enzymes; a deficiency can lead to heart and bone problems and in children, stunted growth. However, it has been known since 1837 that workers in manganese mines can develop *manganism*, a dreaded illness marked by Parkinson’s-like tremors, violent outbursts, and hallucinations. When manganese (this should be manganese oxide) is inhaled, blood ferries it from the lungs to the brain, where it can readily cross the blood-brain barrier. As stated before, **excess manganese ions in the brain should lead to the deficiency of neurotransmitters**, and this should give the most reasonable explanation for the

“manganism” observed. Several studies have demonstrated that iron deficiency increases transport of orally administered manganese into the body as well as delivery to the brain. (Aschner *et al.* Ann. NY Acad Sci. 1012(2004), 115; Gunter *et al.*, NeuroToxicology, 27(2006), 765; Erickson and Aschner, NeuroToxicology, 27(2006)). Many countries in the world completed phasing out leaded gasoline (gasoline containing tetraethyl-lead), paving the way for widespread use of a manganese-based compound, MMT, in gasoline. (MMT=methyl cyclopentadienyl manganese tricarbonyl). ***This means that manganese oxide, one of the famous chemical carcinogens, is widely spread in the sky, and the human inhale the manganese oxide every day, which is stored in the lung. The use of MMT should be stopped as soon as possible!***

Non-specific Iron ion and Abnormalities in Brain Iron Metabolism

It is known that ferritin is taken up by lysosomes, and that subsequent processing involved a partial dissolution of the core, and degradation to siderosomal ferritin and to the insoluble haemosiderin. Thus the haemosiderin from various iron-loaded animals were consistently found to *have ferrihydrite-like iron cores* similar to ferritin, and haemosiderin is typically insoluble, as isolated, in contrast to the soluble ferritin, but it can be solubilized by the *several amino acids or small peptides*, to give ***so-called non-specific iron ions, which exist in brain as soluble dimeric (or polymeric) compound.*** *It should be noted here that these binuclear iron (III) compounds are highly toxic, giving rise to increased oxidation of lipids, proteins, DNA damages, and also cell death in the presence of hydrogen peroxide.*

Summary

Based on our investigation for the chemical mechanism of pathogenesis of *sporadic prion diseases and ALS, and other neurodegenerative disorders*, it is clear that one of the most important risk factor to induce these diseases is the abnormal accumulation of Al(III) or Mn(II) ions in brain, which leads to the abnormalities in brain iron metabolism, *i.e.*, formation of non-specific iron ions, which subsequently leads to the cell-death.

Thus, we must pay attention to the meals and foods in our daily life in order to prevent the increases of Al³⁺ and Mn²⁺ ions in brain, which should be quite effective to decrease or prevention of mental diseases such as depression, schizophrenia, and violent or rough children, etc. We also must adopt adequate countermeasures for “acid rain”. I already proposed new methods to maintain the healthy forests and woods in Japan, which should be the best way towards the acid rain. Strong acid rain dissolves out the iron ions from the surface of the mountains and hills, leading to iron-deficiency in many trees, which should be a critical origin for the abnormal autumn tints frequently observed in recent Japan.