Chapter 21

Zinc and Neurodegenerative Diseases

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1. Introduction

Zinc (Zn) is an essential trace element for most organisms. It plays important roles in various physiological functions such as the mitotic cell division, the immune system, the synthesis of proteins and DNA as a co-factor of more than 300 enzymes or metalloproteins [1]. Recent studies revealed that Zn signaling plays crucial roles in various biological systems of humans [2]. Zn deficiency in human childhood is known to cause the dwarfism, the retardation of mental and physical development, the immune dysfunction, and the learning disabilities [3]. In adults, Zn deficiency causes the taste and odor disorders.

The human body contains approximately 2 g of Zn, mostly in the testes, muscle, liver, and brain tissues. In the brain, Zn is found at the highest concentrations in the hippocampus, amygdala, cerebral cortex, thalamus, and olfactory cortex [4]. The total Zn content of the hippocampus is estimated to be 70–90 ppm (dry weight). Although some Zn in the brain binds firmly to metalloproteins or enzymes, a substantial fraction (approximately 10% or more) either forms free Zn ions (Zn^{2+}) or is loosely bound, and is histochemically detectable by staining using chelating reagents. This chelatable Zn is stored in presynaptic vesicles of specific excitatory glutamatergic neurons and is secreted from these vesicles into synaptic clefts along with glutamate during neuronal excitation. Recent studies have suggested that this secreted Zn^{2+} plays crucial roles in information processing, synaptic plasticity, learning, and memory (Fig. 1A). Indeed, Zn^{2+} in the hippocampus is essential for the induction of long-term potentiation (LTP), a form of synaptic information storage that has become a well-known paradigm for the mechanisms underlying memory formation [5].

However, despite its importance, excess Zn is neurotoxic and implicated in neurodegenerative diseases. In this chapter, we review the current understanding about the link between the disruption of Zn homeostasis and the pathogenesis of various neurodegenerative diseases including senile dementia.

2. Zinc and vascular type of dementia

2.1. Zn-induced neurodegeneration after ischemia

Senile dementia is a serious problem in a rapidly aging world. Its prevalence increases with age. Approximately 25% of elderly individuals are affected by the diseases. In Japan, 3 million people have been estimated to be affected by senile dementia by 2025, and the number continues to grow annually. Senile dementia is mainly divided to Alzheimer's disease (AD) and vascular-type dementia (VD). VD is a degenerative cerebrovascular disease, and its risk factors include aging, sex difference (male), diabetes, and high blood pressure. The most common type of VD is caused by a series of small strokes or ischemia [6]. Following transient global ischemia or stroke, the interruption of blood flow and the resulting oxygen-glucose deprivation induce long-lasting membrane depolarization and cause an excessive release of glutamate into synaptic clefts. Thereafter, the excess glutamate causes over-stimulation of its receptors, namely, *N*-methyl-D-aspartate (NMDA)-type receptors, amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type receptors, and kainite-type receptors. Finally, Ca^{2+} dyshomeostasis, *i.e.*, the entry of large quantities of Ca^{2+} occurring in glutamate-responsive neurons, triggers the delayed death of vulnerable populations of neurons such as pyramidal neurons in the hippocampus —an area associated with learning and memory. Thereafter, the development of an infarct and the subsequent cognitive dysfunction mark the pathogenesis of VD in elderly people. Approximately 30% of stroke patients show symptoms of dementia within 3 months of the initial stroke [7].

Increasing evidence suggests that Zn is central to ischemia-induced neuronal death and finally the pathogenesis of VD [8]. In ischemic conditions, a considerable amount of Zn (up to 300μM) is co-released with glutamate into synaptic clefts by membrane depolarization. Zn caused the apoptotic death of primary cultured cortical neurons. Furthermore, the chelatable Zn reportedly moved from presynaptic terminals into postsynaptic neuronal cell bodies. The increase in intracellular Zn^{2+} levels ($[Zn^{2+}]_i$), namely, "Zn translocation," occurs in vulnerable neurons in the CA1 or CA3 regions of the hippocampus prior to the onset of the delayed neuronal death after transient global ischemia [9]. This Zn translocation is reported to enhance the appearance of the infarct. Administration of calcium EDTA (Ca EDTA), a membrane-impermeable chelator that chelates cations except for calcium, blocked the translocation of Zn, protected the hippocampal neurons after transient global ischemia, and reduced the infarct volume [10]. Thus, Zn translocation is recognized to be the primary event in the pathway of Zn-induced neuronal death. Sensi *et al.* observed a temporal change of $[Zn^{2+}]_i$ in cultured cortical neurons using a zinc-sensitive fluorescent dye; those results revealed that at least three major routes of Zn^{2+} entry have been identified; voltage-gated Ca^{2+} channels (VGLC), NMDA-type glutamate receptors (NMDA-R), and AMPA/kainite-type glutamate receptors (A/K-R). Although the NMDA-type glutamate receptors are present in most neu-

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rons, the permeablity of Zn^{2+} and Ca^{2+} through AMPA/kainate channels is greater than NMDA-receptor channels [11].

In a normal condition, most hippocampal neurons express AMPA receptors with subunit GluR2, which are poorly permeable to divalent cations including Ca^{2+} and Zn^{2+}(A/K-R). However, after ischemia, the acute reduction in the expression of GluR2 subunit occurs, and neurons possess specific type of AMPA receptors which channels are directly Ca^{2+} permeable (Ca-AMPA/kainate channels; Ca-A/K-R)) [12]. The appearance of Ca-AMPA/kainate channels causes the increased permeability of Ca^{2+} and enhances the toxicity. Therefore, the expression of Zn^{2+}-permeable Ca-AMPA/kainite channels and the entry of Ca^{2+} and/or Zn^{2+} through the channels are mediators of the delayed neuronal death after ischemia. Considering that Ca EDTA, a zinc chelator, attenuates the ischemia-induced down-regulation of GluR2 gene [10], Zn is also implicated in the transcriptional regulation in Ca-AMPA/kainite channels.

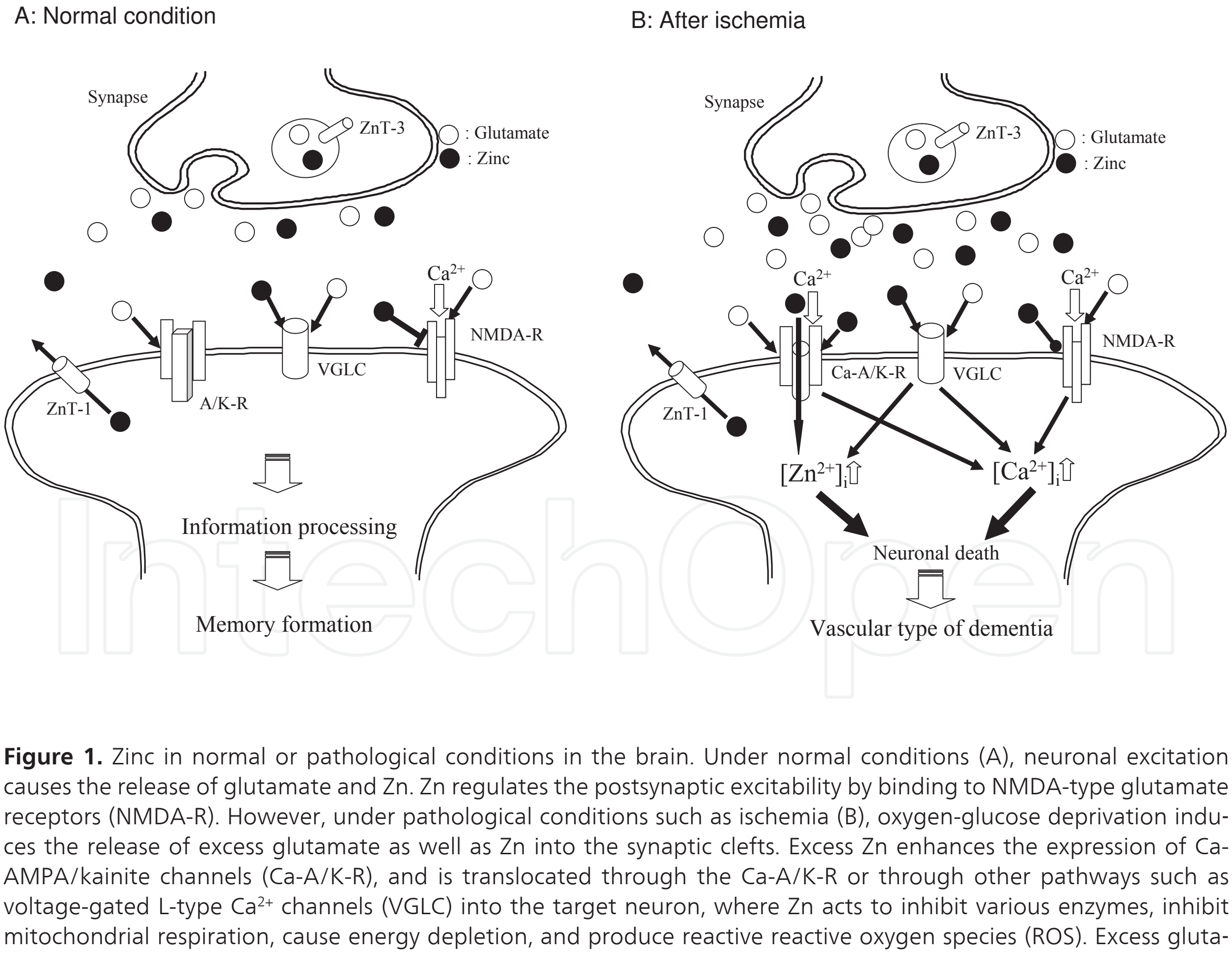

Figure 1. Zinc in normal or pathological conditions in the brain. Under normal conditions (A), neuronal excitation causes the release of glutamate and Zn. Zn regulates the postsynaptic excitability by binding to NMDA-type glutamate receptors (NMDA-R). However, under pathological conditions such as ischemia (B), oxygen-glucose deprivation induces the release of excess glutamate as well as Zn into the synaptic clefts. Excess Zn enhances the expression of Ca-AMPA/kainite channels (Ca-A/K-R), and is translocated through the Ca-A/K-R or through other pathways such as voltage-gated L-type Ca^{2+} channels (VGLC) into the target neuron, where Zn acts to inhibit various enzymes, inhibit mitochondrial respiration, cause energy depletion, and produce reactive reactive oxygen species (ROS). Excess glutamate induces elevation of intracellular Ca^{2+} levels in the target neuron. Elevated levels of intracellular Ca^{2+} then trigger various apoptotic pathways such as the activation of calpain, caspases or other enzymatic pathways related to apoptosis; ultimately this leads to neuronal death.

Zn-specific membrane transporter proteins (Zn transporters) also control Zn homeostasis; they facilitate zinc influx in deficiency and efflux during zinc excess. Recent genetic and molecular approaches revealed the implications of abnormalities in Zn transporters in various human diseases [13]. Zn transporter 1 (ZnT-1), a membrane protein with six transmembrane domains, is widely distributed in mammalian cells, and is co-localized with chelatable Zn in the brain. ZnT-1 is activated by excess Zn and the expression of ZnT-1 is induced after transient global ischemia. On the contrary, dietary Zn deficiency decreases expression of ZnT-1. Consequently, it is provable that ZnT-1 plays a pivotal role in efflux of Zn and in protection from Zn toxicity. Another important Zn transporter in the brain is ZnT-3, which localizes in the membranes of presynaptic vesicles, transports Zn into synaptic vesicles, and maintains high Zn concentrations in the vesicles. Although the physiological role of ZnT-3 and vesicular zinc remain elusive, recent studies have suggested the implication of ZnT-3 or other Zn transporters in the pathogenesis of AD and other neurodegenerative diseases [14].

2.2. Molecular mechanism of Zn-induced neurotoxicity: GT1-7 cells as an *in vitro* model system

Understanding the molecular mechanism of Zn-induced neuronal death is of great importance for the treatment of VD. Numerous studies have been undertaken to elucidate the mechanism of Zn-induced neuronal death. To this end, many researchers have investigated Zn neurotoxicity *in vitro* mainly using primary cultured neurons from rat cerebral cortex or hippocampus [15] or PC-12 cells, a pheochromocytoma cell line [16]. However, the roles of Zn are highly complex. For example, Zn reportedly inhibits NMDA-type glutamate receptors and regulates the excitability of glutamatergic neurons, which are toxic to neurons. Therefore, distinguishing of the effects of Zn and glutamate by using neuronal cells which possess glutamate receptors has proved difficult.

We found that GT1-7 cells, immortalized hypothalamic neurons, are much more sensitive to Zn than other neuronal cells are [17,18] (Fig. 2A). Zn caused the apoptotic death of GT1-7 cells in a dose-dependent and time-dependent manner. The degenerated GT1-7 cells were terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick-end labeling (TUNEL) positive and exhibited the DNA fragmentation.

The GT1-7 cells were originally developed by Mellon *et al.* by genetically targeting tumorigenesis of mouse hypothalamic neurons [19]. The cells possess neuronal characteristics such as the extension of neurites, secretion of gonadotropin-releasing hormone (GnRH), and expression of neuron-specific proteins or receptors including microtubule-associated protein 2 (MAP2), tau protein, neurofilament, synaptophysin, $GABA_A$ receptors, dopamine receptors, and L-type Ca^{2+} channels. Additionally, the GT1-7 cells either lack or possess low levels of ionotropic glutamate receptors and do not exhibit glutamate toxicity [20]. These properties make the GT1-7 cell line an excellent model system for the investigation of Zn-induced neurotoxicity.

We investigated the detailed characteristics of Zn-induced death in GT1-7 cells and its mechanisms. First, we tested the effects of various pharmacological agents prior to Zn treatment of GT1-7 cells. Neither antagonists nor agonists of excitatory neurotransmitters (D-APV, glutamate, and CNQX), or those of inhibitory neurotransmitters (bicuculline, muscimol, baclofen, and GABA) attenuated the viability of GT1-7 cells after Zn exposure. Our findings in GT1-7 cells, which lack such glutamate receptors, are inconsistent with previous studies that agonists of glutamate receptors, such as NMDA or AMPA, enhance Zn-induced neurotoxicity in cultured cortical neurons [21].

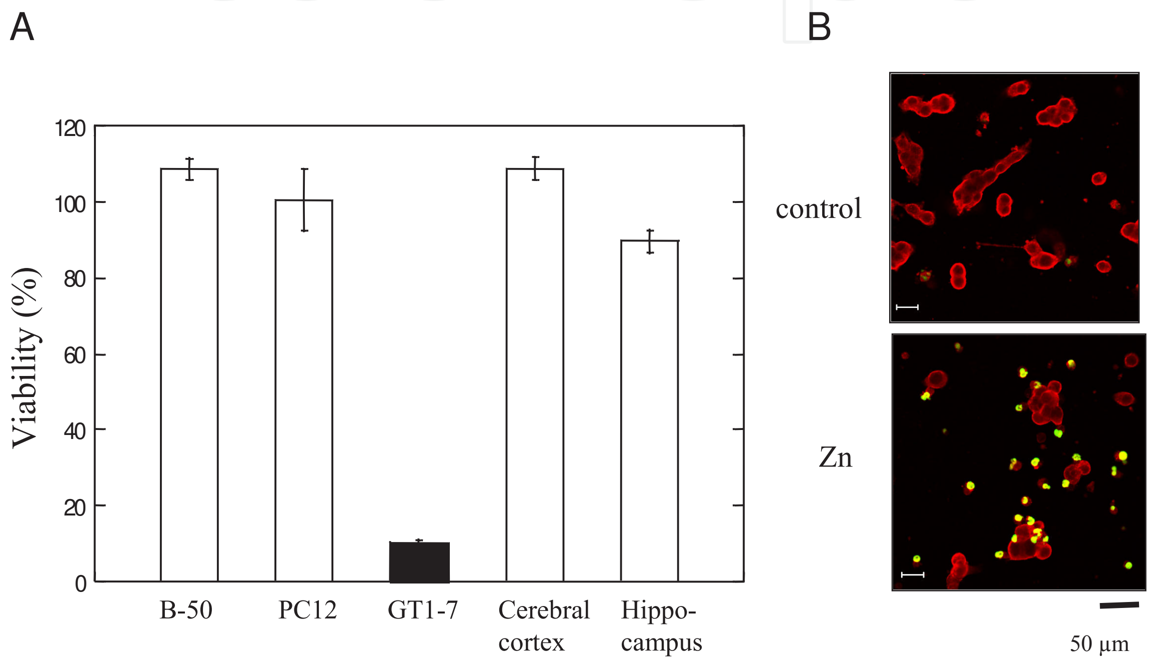

Figure 2. Apoptotic death of GT1-7 cells after exposure to Zn. A: Viability of various neuronal cells after exposure to Zn. Cultured neuronal cells (GT1-7 cells, PC-12 cells, B-50 cells (a neuroblastoma cell line), primary cultured neurons of the rat cerebral cortex, and primary cultured neurons of the rat hippocampus) were administered to 50 µM of Zn. After 24h, cell viability was analyzed by WST-1 method. B: TUNEL staining of Zn intoxicated GT1-7 cells GT1-7 cells were exposed to 50 µM Zn, and were observed with TUNEL staining after 24h.

To evaluate the involvement of other metal ions in Zn neurotoxicity, we investigated the viability of GT1-7 cells with or without various metal ions after exposure to Zn [22]. The equimolar addition of Al^{3+} and Gd^{3+} significantly inhibited Zn-induced neurotoxicity. Moreover, overloading of Ca^{2+} and Mg^{2+} inhibited the Zn-induced death of GT1-7 cells; Zn protected GT1-7 cells from neurotoxicity induced by Ca^{2+} overload, and *vice versa* (Fig. 3B). Furthermore, Kim *et al.* reported that Zn neurotoxicity in PC-12 cells was attenuated by an L-type Ca^{2+} channel blocker, nimodipine, and enhanced by the L-type Ca^{2+} channel activator, S(-)-Bay K 8644 [16]. Additionally, Zn neurotoxicity was attenuated by aspirin, which prevents Zn^{2+} entry through voltage-gated Ca^{2+} channels. These pharamacological evidence suggests that Ca dyshomeostasis is involved in the mechanism of Zn-induced neurotoxicity.

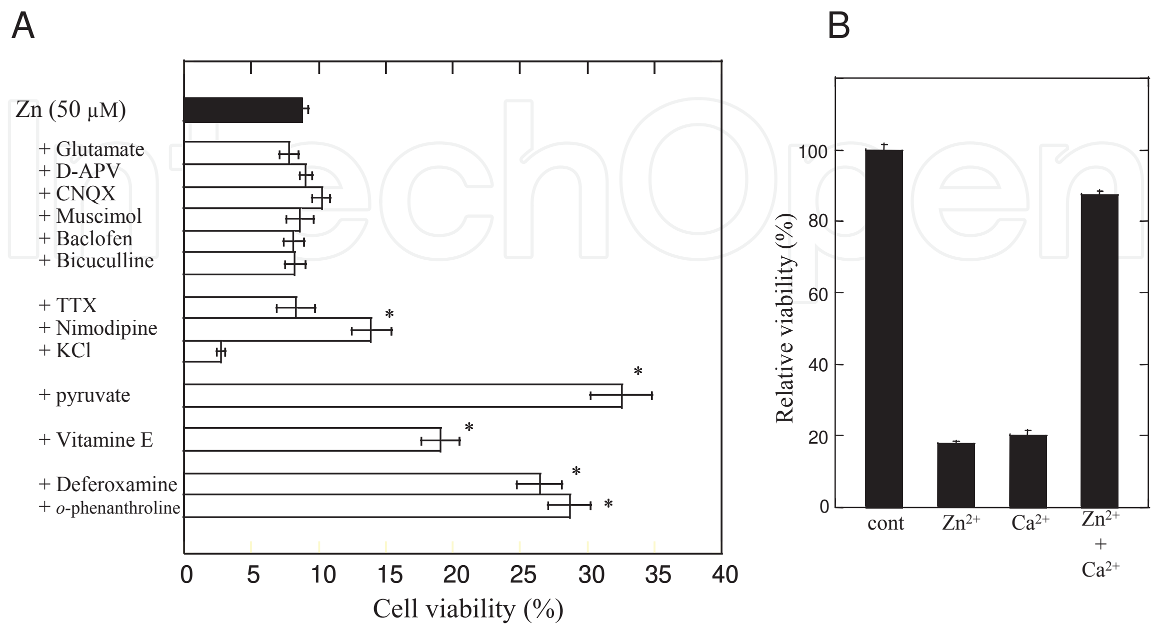

Figure 3. Effects of various pharmacological substances on Zn-induced death of GT1-7 cells. A: GT1-7 cells were exposed to 50μM of Zn^{2+} with agonists or antagonisits of neurotransmitters (D-APV (D-2-amino-5-phosphonovalerate), glutamate, CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), bicuculline, muscimol, baclofen, GABA (gamma-aminobutyric acid)), channel blockers (TTX(tetrodotoxin), nimodipine), etc. B: GT1-7 cells were exposed to Zn^{2+} with or without Ca^{2+}.

2.3. Implication of Ca dyshomeostasis in Zn-induced neuronal death

To address this issue, we employed a high-resolution multi-site video imaging system with fura-2 as the cytosolic free calcium reporter fluorescent probe for the observation of temporal changes in $[Ca^{2+}]_i$ after exposure to Zn (Fig. 4). This multisite fluorometry system enables the simultaneous long-term observation of temporal changes in $[Ca^{2+}]_i$ of more than 50 neurons. The elevations in $[Ca^{2+}]_i$ were observed among GT1-7 cells after 3-30 min of the exposure to Zn [18]. Detailed analysis of Zn-induced $[Ca^{2+}]_i$ revealed that pretreatment of Al^{3+} significantly blocked the Zn-induced $[Ca^{2+}]_i$ elevations. Thus, it is possible that Al^{3+}, a known blocker of various types of Ca^{2+} channels, attenuate Zn-induced neurotoxicity by blocking Zn-induced elevations in $[Ca^{2+}]_i$.

We also showed that the administration of sodium pyruvate, an energy substrate, significantly inhibited the Zn-induced death of GT1-7 cells [17]. The results are consistent with findings of other studies using primary cultured cortical neurons, oligodendrocyte progenitor cells, or retinal cells. Furthermore, the administration of pyruvate attenuated the neuronal death after ischemia *in vivo* [23]. Shelline and his colleagues reported that Zn exposure decreased the levels of NAD^+ and ATP in cultured cortical neurons, and that treatment with pyruvate restored the NAD^+ level [24]. An imaging study using a Zn-sensitive fluorescent dye and a mitochondrial marker revealed that Zn is localized within mitochondria. Zn is reported to inhibit various mitochondrial enzymes and the intracellular trafficking of mitochondria. It has also been reported that Zn produced ROS and caused oxidative damage resulting from mitochondrial impairments. Therefore, energy failure and the inhibition of glycolysis in mitochondria may be involved in Zn neurotoxicity [25].

2.4. Carnosine as an endogenous protective substance against Zn neurotoxicity

Considering the implication of Zn in transient global ischemia, substances that protect against Zn-induced neuronal death could be potential candidates for the prevention or treatment of neurodegeneration following ischemia, and ultimately provide a lead to treatments for VD. With the aim of exploring this idea, we developed a rapid, sensitive, and convenient assay system for the mass-screening of such substances by using GT1-7 cells. We examined the potential inhibitory effects of various agricultural products such as vegetable extracts, fruits extracts, and fish extracts, and found that extracts from eel muscles significantly protected against Zn-induced neurotoxicity [26]. Finally, we demonstrated that carnosine (ß-alanyl histidine), a small hydrophilic peptide abundant in eel muscles, protected GT1-7 cells from Zn-induced neurotoxicity in a dose-dependent manner. Therefore, we applied for the patent on carnosine as a drug for the treatment of VD or for slowing the progress of cognitive decline after ischemia (the application No. 2006-145857; the publication No. 2007-314467 in Japan) [27]. Carnosine is a naturally occurring dipeptide and is commonly present in vertebrate tissues, particularly within the skeletal muscles and nervous tissues [28]. It is found at high concentrations in the muscles of animals or fish which exhibit high levels of exercise, such as horses, chickens, and whales. The concentration of carnosine in the muscles of such animals is estimated to be 50–200 mM, and carnosine is believed to play important roles in the buffering capacities of muscle tissue. During high-intensity anaerobic exercise, proton accumulation causes a decrease in intracellular pH, which influences various metabolic functions. The p*K*a value of carnosine is 7.01, close to intracellular pH.

Therefore, carnosine contributes to physicochemical non-bicarbonate buffering in skeletal muscles, and the administration of carnosine has been reported to induce hyperactivity in animals.

Carnosine reportedly has various functions including anti oxidant, anti glycation, anti crosslink, and considered to be an endogenous neuroprotective, anti-aging substances. Considering the advantegeous properties of carnosine Considering the advantegeous properties of carnosine (relatively non-toxic, heat-stable, and water-soluble), the dietary supplementation of carnosine might be an effective strategy for the prevention or treatment of neurodegenerative diseases such as ischemia, VD, AD, and prion diseases. Corona et al. reported that supplementation of carnosine improved learning abilities of Alzheimer's model mice [29]. We demonstrated that neurotoxicity of prion protein fragment was attenuated by Zn and carnosine [30].

3. Zn and Alzheimer's disease diseases

3.1. Amyloid cascade hypothesis and Zn

AD is a severe senile type of dementia first reported in 1906. The pathological hallmarks of AD are the deposition of extracellular senile plaques, intracellular neurofibrillary tangles (NFTs), and the selective loss of synapses and neurons in the hippocampal and cerebral cortical regions. The major component of NFTs is the phosphorylated tau protein. Senile plaques are largely comprised of ß-amyloid protein (AßP) [31]. Numerous biochemical, toxicological, cell biological, and genetic studies have supported the idea termed "amyloid cascade hypothesis" which suggests that the neurotoxicity caused by AßP play a central role in AD [32,33]. AβP is a small peptide with 39–43 amino acid residues. It is derived from the proteolytic cleavage of a large precursor protein (amyloid precursor protein; APP). AβP has an intrinsic tendency to self-assemble to form sodium dodecyl sulfate (SDS)-stable oligomers. Moreover, oligomerization and conformational changes in AßP are important for its neurodegeneration process. In an aqueous solution, freshly prepared and dissolved AβP exists as a monomeric protein with a random coil structure. However, following incubation at 37°C for several days (*aging*), AβPs form aggregates (oligomers) with β-pleated sheet structures, and finally form insoluble aggregates, termed amyloid fibrils (Fig. 5). The *aged* AβP peptides were considerably more toxic to cultured neurons than *fresh* (freshly prepared just before the experiment) AβP. AßP is secreted in the cerebrospinal fluid (CSF) of young individuals as well as in aged or dementia patients [34]. Therefore, factors that accelerate or inhibit the oligomerization may play essential roles in the pathogenesis of AD. Several factors such as the concentration of peptides, pH, composition of solvents, temperature, oxidations, mutations, and racemization of AßP can influence the oligomerization processes [35].

Interestingly, rodent AßP exhibits less tendency to oligomerization than human AßP *in vitro* and the accumulation of AßP is rarely observed in the brains of rodents (rats or mice) as compared to primates (humans or monkeys). As shown in Fig. 5, the amino acid sequences of human and rodent AßP are similar, but rodent AßP differs from primate only 3 amino acids (Arg^5, Tyr^{10}, and His^{13}) from primate AßP. All three amino acids have the ability to bind metals. Therefore, trace elements including Al, Zn, Cu, Fe as the accelerating factor of AßP are of particularly interest.

We have investigated the metal-induced oligomerization of AßP and found that the metals including Al, Zn, Fe, Cu, and Cd enhanced the oligomerization. However, the oligomerization induced by Al is more marked than that induced by other metals [36,37]. Furthermore, while Zn-aggregated AßPs are rarely observed on the surface of cultured neurons several days after its exposure, Al-aggregated AßPs bind tightly to the surface of cultured neurons and form fibrillar deposits. Bush et al. reported the Zn- or Cu- induced oligomerization of AßP [38,39], and have developed the chelation therapy for AD treatment [40]. Clioquinol (quinoform), a chelator of Cu^{2+} or Zn^{2+}, inhibits oligomerization of AßP and attenuates the accumulation of amyloid in the brains of experimental animals. Clinical trials using its analogue PBT2 are under investigation. However, considering that the morphology of AßP oligomers treated with metals including Al, Cu, Fe, Zn are quite different [41] and that re-

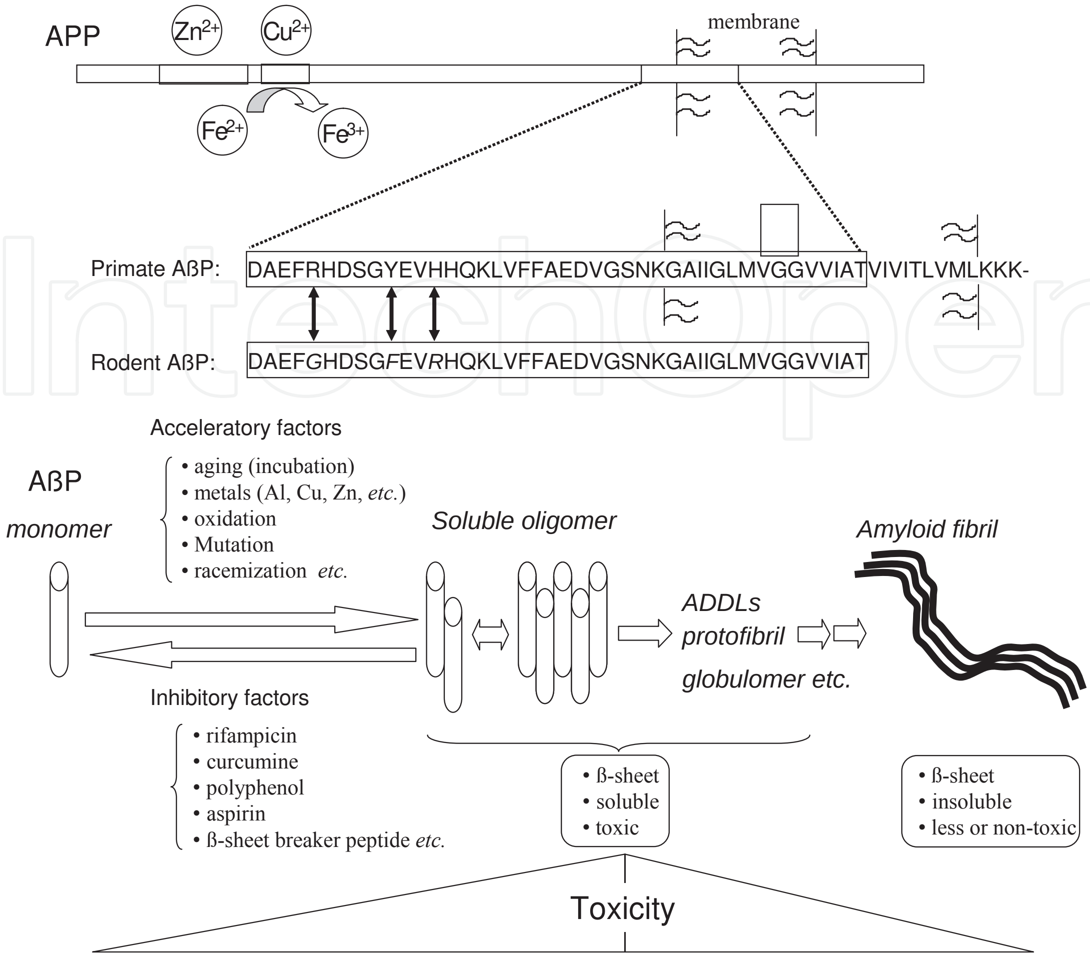

Figure 5. Amyloid cascade hypothesis and the implications of Zn and other metals. AßP is secreted from its precursor APP, a Zn- or Cu- binding protein. AßP monomers exhibit random-coil structures. However, during aging or in the presence of some acceleratory factors, AßP self-aggregates and forms several types of oligomers (SDS-soluble oligomers, ADDLS, globulomers, protofibrils, etc.) and finally forms insoluble aggregates, which are termed amyloid fibrils. Oligomeric soluble AßP s are toxic, although monomers and fibrils are rather nontoxic.

cent approaches using size-exclusion chromatography, gel electrophoresis, and atomic force microscopy have demonstrated that identified soluble oligomers are neurotoxic, further studies about metal-induced oligomerization are necessary.

APP also possesses copper/zinc binding sites in its amino-terminal domain and in the AßP domain and may be involved in homeostasis of these metals [42]. Duce *et al.* demonstrated that APP has ferroxidase activity, which converts Fe^{2+} to Fe^{3+} and regulates free pro-oxidant Fe^{2+} concentrations. They also found that Zn^{2+} inhibits the ferroxidase activity of APP [43]. Thus, the interaction with Zn and other metals in the functions of APP are of great interst.

3.2. AßP -induced neuronal death and Zn

Zn is involved in the mechanism of AßP-induced neurotoxicity. There is considerable interest regarding the mechanism by which AßPs cause neuronal death. In 1993, Arispe *et al.* first demonstrated that AßP directly incorporates into artificial lipid bilayer membranes and forms cation-selective (including Ca^{2+}) ion channels [44,45]. We revealed that AßP formed amyloid channels on the GT1-7 cell membranes and their characteristics were considerably similar to those observed on artificial lipid bilayers; cation-selective, multilevel [46]., and that AßP causes the increase of intracellular Ca^{2+} in GT1-7 cells and degeneration [47]. These results strongly support the hypothetical idea termed 'amyloid channel hypothesis', namely, that the direct incorporation of AßPs and the subsequent imbalances of Ca^{2+} and other ions through amyloid channels may be the primary event in AßP neurotoxicity [48].

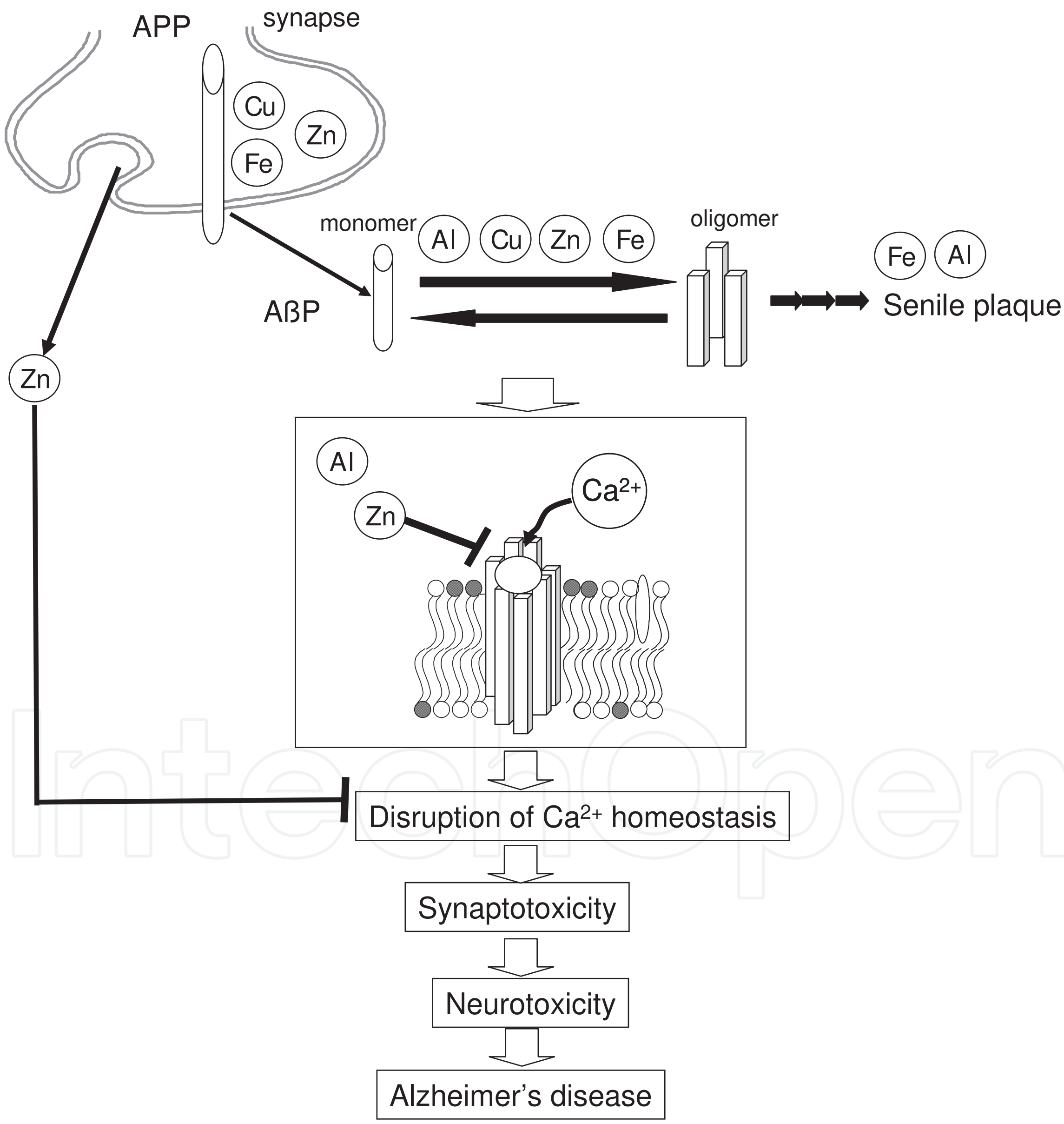

Figure 6. Zn and other metals in the pathogenesis of Alzheimer's disease. Details are shown in the text.

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Inorganic cations such as Al^{3+} or Zn^{2+} inhibit current induced by amyloid channels [44,45]. Zn reportedly inhibited AßP-induced Ca^{2+} increase. We have revealed that the amyloid channel activity formed on membranes of GT1-7 cells was inhibited by addition of Zn^{2+}, and recovered by Zn chelator, *o*-phenanthroline [47]. Considering that Zn binds to His residues of AßP, Arispe *et al.* found that histidine-related peptide derivatives such as His-His are effective in the inhibition of amyloid channels, the attenuation of AßP-induced $[Ca^{2+}]_i$ changes, and the protection of neurons from AßP toxicity. Among various compounds tested, small amphiphilic pyridinium salts were revealed to block the amyloid channel and protect neurons [49].

Based on our and other findings about the link between Zn and the pathogenesis of AD, we made a hypothetical scheme about the link between AD pathogenesis and Zn (Fig. 6). AßPs are normally secreted from APP, which exists in the synapse. Secreted AßPs are usually degraded proteolytically by proteases within a short period. However, Zn or other metals enhance the oligomerization and accumulation of AßP. After incorporation into the membrane, the conformation of AßPs change and the accumulated AßPs aggregate on the membranes.. Finally, aggregated AßP oligomers form ion channels leading to the various neurodegenerative processes.Unlike endogenous Ca^{2+} channels, these AßP channels are not regulated by usual blockers. Thus, once formed on membranes, a continuous flow of $[Ca^{2+}]_i$ is initiated. Disruption of calcium homeostasis triggers several apoptotic pathways and promotes numerous degenerative processes, including free radical formation and tau phosphorylation, thereby accelerating neuronal death. Meanwhile, Zn^{2+}, which are secreted into synaptic clefts in a neuronal activity-dependent manner, inhibit AßP-induced Ca^{2+} entry, and thus have a protective function in AD.

4. Conclusion

Based on results of our own and other numerous studies, the disruption of Zn homeostasis, namely both zinc depletion and excess zinc, cause severe damage to neurons and linked with various neurodegenerative diseases including VD and AD. Increasing evidence suggests the implications of Zn in the pathogenesis of other neurodegenerative disease including prion diseases, Parkinson disease, ALS etc. Zn acts as a contributor of the disease in one part, and as a protector in another part. Thus, Zn might play a role like that of Janus, an ancient Roman god of doorways with two different faces, in the brain (Fig. 7).

Our new approach to ischemia-induced neurodegeneration from the perspective of the Zn hypothesis will lead to new therapeutic tools for the treatment and/or prevention of VD. Further research about the role of Zn in neuronal injury and the significance of Zn homeostasis might give rise to the development of new treatments for neurodegenerative diseases. In this context, the advantegeous properties of carnosine (relatively non-toxic, heat-stable, and water-soluble) as a possible candidate for the prevention or treatment of neurodegenerative diseases such as ischemia, VD, AD, and prion diseases are important.

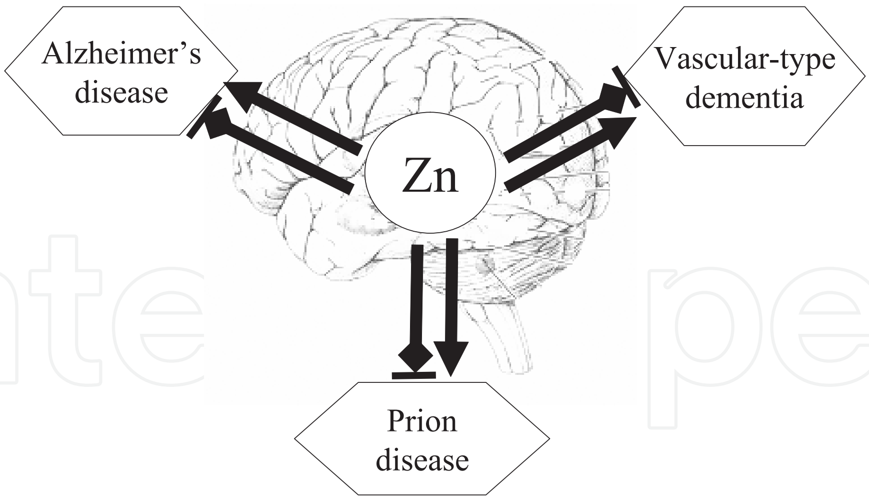

Figure 7. Zn as Janus in brain

As described here, Zn plays important roles in memory formation, and protects neurons from various neurodegenerative diseases. Meanwhile, excess Zn is neurotoxic and may enhance the pathogenesis of the diseases.

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