Review

Disruption of brain zinc homeostasis promotes the pathophysiological progress of Alzheimer's disease

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Summary. Zinc is abundant in the brain, where it plays an important role in synaptic plasticity and in learning; however, excessive zinc is toxic to neuronal cells, and dyshomeostasis of zinc in the brain is a contributing factor for Alzheimer's disease (AD). Deposition of zinc has been detected in senile plaques in the form of zinc-Aβ (β-amyloid) complexes. Recent studies have demonstrated that zinc exposure to the brain enhances β-amyloid precursor protein (APP) expression, amyloidogenic APP cleavage and plaque burden. Furthermore, alterations in zinc transporters, which are responsible for zinc homeostasis, occur in AD human brain and transgenic mouse models. These suggest that abnormal brain zinc homeostasis is involved in the patho-physiological progress of AD.

Key words: Alzheimer's disease, Divalent metal transporter 1, Metal chelator, Zinc, Zinc transporter

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that represents the most common form of dementia in the elderly. Along with disease progression, the clinical characteristics of AD include short-term memory loss, problems with language, disorientation, mood swings, and mismana-gement of self-care. The pathological features of AD include β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles, loss of neurons and synapses, and activation of glia cells. A primary theory for the cause of AD is the "Aβ deposition theory". Aβ is derived from a transmembrane protein, the β-amyloid precursor protein (APP), by the action of two cleavage enzymes that are referred to as β- and γ-secretases (Haass et al., 1992; Seubert et al., 1992; Shoji et al., 1992). This process is called amyloidogenesis. Finally, Aβ is toxic and may cause neuronal death in the case of AD.

Recently, several groups have raised the "metal hypothesis" of AD (Duce and Bush, 2010). This hypothesis is mainly based upon experimental results. First, several metal ions, such as zinc, iron and copper, are all increased in the ageing brain. It has been reported that the content of metal ions in the brain of AD patients is 3-7 times that of normal people and that the metal ions in brain homeostasis may result in the development of AD (Zatta et al., 2009). Second, these metal ions can interact with Aβ, resulting in the promotion of Aβ deposition and plaque formation. For example, zinc can bind to Aβ molecules through the histidine residue (Liu et al., 1999). Third, some proteins that are related to amyloidogenesis, including APP, β- and γ-secretase, are all ion-binding proteins. Finally, the use of metal chelators, such as clioquinol, deferoxamine and trientine, is beneficial for AD patients and attenuates Aβ deposition in AD animal models (Ritchie et al., 2003; Wang et al., 2012, 2013; Guo et al., 2013a,b, 2015). Therefore, abnormal metal metabolism has an important

role in Aβ generation and accumulation in the brain.

It is well known that metal ions cannot freely pass through the membrane structure. In the plasma membrane, there are several metal transporters that are responsible for metal ion transportation. For example, divalent metal transporter 1 (DMT1) is a divalent metal ion transporter and the zinc transporters (ZnTs) family is responsible for zinc transmembrane transportation (Fleming et al., 1997; Gunshin et al., 1997; Kambe et al., 2015). Several studies have shown that changes in expression levels and distribution of these metal transporters have been found in the AD brain. This suggests that metal transporters might be involved in dyshomeostasis of metal ions as well as in Aβ secretion and deposition. Furthermore, metal chelators may be a potential strategy for AD prevention and therapy.

Zinc is abundant in senile plaques

Zinc is an essential element and has many important biological functions in the body. In the brain, approximately 85% of zinc ions bind with the metal proteins or nucleic acids, while 15% of zinc ions are present as free or loosely bound ions (Wang et al., 2002). The average content of free zinc ions in the brain is approximately 150 μmol/L, which is approximately 10 times the level of serum zinc (Takeda, 2000; Weiss et al., 2000). Free zinc ions are abundant in the synaptic vesicles in hippocampal mossy fibers, where zinc has an important role in synaptic plasticity, learning and memory (Frederickson and Moncrieff, 1994). Except for its physiological roles, however, excessive zinc is toxic and can result in necrotic, apoptotic and autophagic cell death through the activation of multiple intracellular pathways (Dineley et al., 2003, 2005; Sensi et al., 2003, 2009).

It has been generally accepted that brain zinc dyshomeostasis is involved in neuronal death and the pathogenesis of AD (Maynard et al., 2005; Xu et al., 2011). With age, zinc levels increase in the brain and may contribute to the risk of AD. Several studies have shown that the level of zinc in serum and in the brain are increased in human AD and the APP/presenilin 1 (PS1) transgenic mouse brain. In the postmortem AD brain, a marked accumulation of zinc is found in Aβ plaques, as detected with different technologies (Lovell et al., 1998; Cherny et al., 1999; Suh et al., 2000; Friedlich et al., 2004). For instance, with proton-induced X-ray emission spectroscopic analysis, an increased amount of zinc ions has been confirmed to exist in the hippocampus and amygdala of AD autopsy tissue (Danscher et al., 1997). With autometallography, a zinc-specific histological technique, several groups have reported that zinc ions reside in senile plaques and the cerebral amyloid angiopathy in the AD brain (Stoltenberg et al., 2005; Zhang et al., 2008). *In vitro* studies, including nuclear magnetic resonance spectroscopy, have shown that Aβ peptide has zinc-binding sites (Huang et al., 2004), and zinc could rapidly destabilize human Aβ1-40 solutions (Bush et al., 1994). Together, the enrichment of zinc ions in plaques indicates that zinc might promote Aβ deposition and the formation of senile plaques.

Zinc accelerates Aβ generation and aggregation

Several studies have demonstrated that both APP and its proteolytic product, Aβ, contain metal binding domains, thereby suggesting that zinc may be involved in APP processing in AD pathological processes. At the cellular level, high zinc treatment enhances amyloidosis through increased β- and γ-secretase cleavage of APP and Aβ secretion in APP Swedish mutant (APPsw) overexpressing cells (Wang et al., 2010). In neonatal mouse cortical culture neurons, exposure of exogenous zinc enhances synthesis of PS1 in a dose-dependent manner (Park et al., 2001). Treatment with high zinc levels in drinking water not only enhances the content of zinc in serum and brain but also leads to an increase in APP expression, amyloidogenic APP cleavage and zinc-containing plaques in the brain of APP/PS1 mice (Wang et al., 2010). Interestingly, treatment with chelator clioquinol prevents cognitive deficits and reduces the expression levels of APP, β- and γ-secretase and the plaque burden in the APP/PS1 mouse brain (Wang et al., 2012). These data demonstrate that excessive zinc exposure to the brain accelerates Aβ generation and aggregation, thereby suggesting that zinc accumulation could be a risk factor for AD progression.

Conversely, studies have shown that zinc supplementation may benefit for AD. In the 3xTg-AD mouse, which is an AD model, the administration of zinc can reduce the pathology of Aβ and tau, increase BDNF levels, and prevent cognitive deficits as well as mitochondrial dysfunction (Corona et al., 2010). Oral zinc treatment reduces insoluble Aβ in the brain of Tg2576 mouse, an AD mouse model (Harris et al., 2014). Therefore, further studies are needed to elucidate the paradoxical role of zinc in AD pathological processes (Cuajungco and Fagét, 2003).

Zinc promotes tau phosphorylation

Free zinc ions are abundant in the synaptic vesicles in hippocampal zinc-containing mossy fibers, which act as a potential neuromodulator during release into the synaptic cleft (Frederickson et al., 2000). Nevertheless, recent studies have demonstrated that synaptic released zinc can promote tau hyperphosphorylation (Boom et al., 2009). For example, zinc treatment causes tau hyperphosphorylation in cultured brain slices, whereas the application of zinc chelators almost abolishes zinc-induced tau hyperphosphorylation (Sun et al., 2012). In the tau transgenic mouse brain, treatment with zinc chelator significantly reduces hyperphosphorylated and insoluble tau levels. Furthermore, the mechanism of zinc-induced tau hyperphosphorylation is related to protein phosphatase 2A inactivation through a Src-dependent pathway (Xiong et al., 2013). In the APP/PS1

transgenic mouse, treatment with iron in drinking water markedly induces tau phosphorylation at the sites of Thr205, Thr231 and Ser396, whereas the administration of the chelator deferoxamine could reduce the levels of tau phosphorylation by suppressing the activities of cyclin-dependent kinase 5 and glycogen synthase kinase 3β (Guo et al., 2013a). It is known that hyperphosphorylated tau is the main component of intracellular neurofibrillary tangles, which can cause microtubule destabilization and neuronal death. Therefore, dyshomeostasis of metal ions, such as zinc and iron, is a critical factor for activating AD pathological processes, not only through interaction with Aβ but also through enhancement of tau hyperphosphorylation (Craddock et al., 2012).

Alterations in zinc transporters in AD brain

The mechanism that involves zinc accumulation in the AD brain has not been fully understood. Recent studies have shown that the abnormal distribution and expression of zinc-regulating metalloproteins may be involved in elevated level of zinc in the AD brain. These metalloproteins include zinc transporters (ZnTs) and divalent metal transporter 1 (DMT1) (Zheng et al., 2009, 2010; Adlard et al., 2010).

Using quantitative real-time PCR, altered mRNA levels of zinc-regulating proteins have been detected in the AD postmortem brain (Beyer et al., 2012). With immunohistochemistry, the distribution of ZnTs, including ZnT1 and ZnT3-7, has been found in the neuritic plaques in the human AD postmortem brain specimens (Zhang et al., 2008). These ZnT proteins could also be found in Aβ plaques in APP/PS1 transgenic mouse brain (Zhang et al., 2010). It is well known that, under physiological conditions, ZnTs are located in the cell membrane and the plasma membrane of the lysosome, Golgi apparatus and synaptic vesicles. Furthermore, the function of ZnTs is to reduce the concentration of zinc in the cytoplasm through the export of zinc to the extracellular space or the transfer of

zinc into cellular organelles from the cytosol (Lichten and Cousins, 2009). Apart from the abnormal distribution of ZnTs in Aβ plaques, the protein expression levels of ZnTs, including ZnT1, 4, and 6, were also found to be altered in the human AD brain (Lovell et al., 2005, 2006). In the APP/PS1 transgenic mouse brain, elevated expression levels of ZnT1, and ZnT3-7 have been observed in the cerebral cortex and hippocampus (Zhang et al., 2010). In ZnT3 knockout and APP overexpressed mice, a marked reduction of Aβ plaque burden and less insoluble Aβ level have been detected in the brain (Lee et al., 2002). Taken together, the abnormal distribution and expression of ZnTs indicates that ZnTs might be important contributing factors for zinc accumulation in senile plaques.

DMT1 is a proton-coupled metal-ion transporter and functions in the uptake of a broad range of divalent metal ions, such as iron, zinc and copper (Fleming et al., 1997; Gunshin et al., 1997). With aging, the expression levels of DMT1 are markedly increased (Ke et al., 2005). Recent studies have shown that the expression levels of DMT1 are significantly increased in the frontal cortex and the hippocampus of the APP/PS1 mouse brain (Zheng et al., 2009; Dong et al., 2015). With confocal microscopy, the colocalization of DMT1 and Aβ has been detected in the senile plaques of the postmortem AD brain and the transgenic mouse brain. More interestingly, *in vitro* studies have shown that a marked reduction in APP expression and Aβ secretion could be found after the silencing of endogenous DMT1 by RNA interference (Zheng et al., 2009). These findings suggest that DMT1 has an important role in ion-mediated neuropathogenesis in AD.

In summary, it can be concluded that dyshomeostasis of brain zinc has an important pathophysiological role in the progress of AD (Fig. 1). Therefore, corrections of zinc metabolism, through applications of metal chelators, might be a feasible therapeutic strategy for AD. Moreover, metal-regulating proteins, such as ZnTs and DMT1, are potential drug targets for the prevention and treatment of AD.
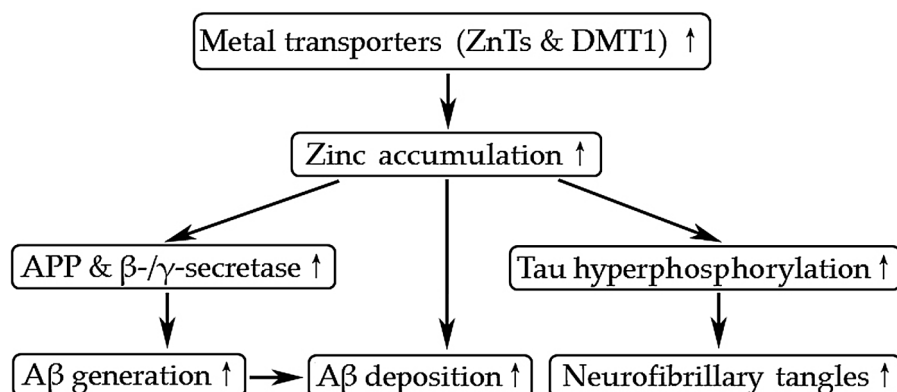

Fig. 1. Involvement of metal transporters and zinc in promotion of AD pathology.

References

Adlard P.A., Parncutt J.M., Finkelstein D.I. and Bush A.I. (2010). Cognitive loss in zinc transporter-3 knock-out mice: a phenocopy for the synaptic and memory deficits of Alzheimer's disease? J. Neurosci. 30, 1631-1636.

Beyer N., Coulson D.T., Heggarty S., Ravid R., Hellemans J., Irvine G.B. and Johnston J.A. (2012). Zinc transporter mRNA levels in Alzheimer's disease postmortem brain. J. Alzheimers Dis. 29, 863-873.

Boom A., Authelet M., Dedecker R., Frédérick C., Van Heurck R., Daubie V., Leroy K., Pochet R. and Brion J.P. (2009). Bimodal modulation of tau protein phosphorylation and conformation by extracellular Zn2+ in human-tau transfected cells. Biochim. Biophys. Acta 1793, 1058-1067.

Bush A.I., Pettingell W.H., Multhaup G., de Paradis M., Vonsattel J.P., Gusella J.F., Beyreuther K., Masters C.L. and Tanzi R.E. (1994). Rapid induction of Alzheimer A beta amyloid formation by zinc. Science 265, 1464-1467.

Cherny R.A., Legg J.T., McLean C.A., Fairlie D.P., Huang X., Atwood C.S., Beyreuther K., Tanzi R.E., Masters C.L. and Bush A.I. (1999). Aqueous dissolution of Alzheimer's disease Abeta amyloid deposits by biometal depletion. J. Biol. Chem. 274, 23223-23228.

Corona C., Masciopinto F., Silvestri E., Viscovo A.D., Lattanzio R., Sorda R.L., Ciavardelli D., Goglia F., Piantelli M., Canzoniero L.M. and Sensi S.L. (2010). Dietary zinc supplementation of 3xTg-AD mice increases BDNF levels and prevents cognitive deficits as well as mitochondrial dysfunction. Cell Death Dis. 1, e91.

Craddock T.J., Tuszynski J.A., Chopra D., Casey N., Goldstein L.E., Hameroff S.R. and Tanzi R.E. (2012). The zinc dyshomeostasis hypothesis of Alzheimer's disease. PLoS One 7, e33552.

Cuajungco M.P. and Fagét K.Y. (2003). Zinc takes the center stage: its paradoxical role in Alzheimer's disease. Brain Res. Brain Res. Rev. 41, 44-56.

Danscher G., Jensen K.B., Frederickson C.J., Kemp K., Andreasen A., Juhl S., Stoltenberg M. and Ravid R. (1997). Increased amount of zinc in the hippocampus and amygdala of Alzheimer's diseased brains: a proton-induced X-ray emission spectroscopic analysis of cryostat sections from autopsy material. J. Neurosci. Meth. 76, 53-59.

Dineley K.E., Richards L.L., Votyakova T.V. and Reynolds I.J. (2005). Zinc causes loss of membrane potential and elevates reactive oxygen species in rat brain mitochondria. Mitochondrion 5, 55-65.

Dineley K.E., Votyakova T.V. and Reynolds I.J. (2003). Zinc inhibition of cellular energy production: implications for mitochondria and neurodegeneration. J. Neurochem. 85, 563-570.

Dong X.H., Gao W.J., Shao T.M., Xie H.L., Bai J.T., Zhao J.Y. and Chai X.Q. (2015). Age-related changes of brain iron load changes in the frontal cortex in APPswe/PS1ΔE9 transgenic mouse model of Alzheimer's disease. J. Trace Elem. Med. Biol. 30, 118-123.

Duce J.A. and Bush A.I. (2010). Biological metals and Alzheimer's disease: implications for therapeutics and diagnostics. Prog. Neurobiol. 92, 1-18.

Fleming M.D., Trenor C.C., Su M.A., Foernzler D., Beier D.R., Dietrich W.F. and Andrews N.C. (1997). Microcytic anaemia mice have a mutation in Nramp2, a candidate iron transporter gene. Nat. Genet. 16, 383-386.

Frederickson C.J. and Moncrieff D.W. (1994). Zinc-containing neurons. Biol. Signals. 3, 127-139.

Frederickson C.J., Suh S.W., Silva D., Frederickson C.J. and Thompson R.B. (2000). Importance of zinc in the central nervous system: the zinc-containing neuron. J. Nutr. 130 (5S Suppl), 1471-1483.

Friedlich A.L., Lee J.Y., van Groen T., Cherny R.A., Volitakis I., Cole T.B., Palmiter R.D., Koh J.Y. and Bush A.I. (2004). Neuronal zinc exchange with the blood vessel wall promotes cerebral amyloid angiopathy in an animal model of Alzheimer's disease. J. Neurosci. 24, 3453-3459.

Gunshin H., Mackenzie B., Berger U.V., Gunshin Y., Romero M.F., Boron W.F., Nussberger S., Gollan J.L. and Hediger M.A. (1997). Cloning and characterization of a mammalian proton-coupled metal-ion transporter. Nature 388, 482-488.

Guo C., Wang P., Zhong M.L., Wang T., Huang X.S., Li J.Y. and Wang Z.Y. (2013a). Deferoxamine inhibits iron induced hippocampal tau phosphorylation in the Alzheimer transgenic mouse brain. Neurochem. Int. 62, 165-172.

Guo C., Wang T., Zheng W., Shan Z.Y., Teng W.P. and Wang Z.Y. (2013b). Intranasal deferoxamine reverses iron-induced memory deficits and inhibits amyloidogenic APP processing in a transgenic mouse model of Alzheimer's disease. Neurobiol. Aging 34, 562-575.

Guo C., Wang T., Zhang Y.X., Wang T., Zhong M.L., Yang Z.H., Hao L.J., Chai R. and Zhang S. (2015). Intranasal deferoxamine attenuates synapse loss via up-regulating the P38/HIF-1α pathway on the brain of APP/PS1 transgenic mice. Front. Aging Neurosci. 7, 104.

Haass C., Koo E.H., Mellon A., Hung A.Y. and Selkoe D.J. (1992). Targeting of cell-surface beta-amyloid precursor protein to lysosomes: alternative processing into amyloid-bearing fragments. Nature 357, 500-503.

Harris C.J., Voss K., Murchison C., Ralle M., Frahler K., Carter R., Rhoads A., Lind B., Robinson E. and Quinn J.F. (2014). Oral zinc reduces amyloid burden in Tg2576 mice. J. Alzheimers Dis. 41, 179-192.

Huang J., Yao Y., Lin J., Ye Y.H., Sun W.Y. and Tang Dagger W.X. (2004). The solution structure of rat Abeta-(1-28) and its interaction with zinc ion: insights into the scarcity of amyloid deposition in aged rat brain. J. Biol. Inorg. Chem. 9, 627-635.

Kambe T., Tsuji T., Hashimoto A. and Itsumura N. (2015). The physiological, biochemical, and molecular roles of zinc transporters in zinc homeostasis and metabolism. Physiol. Rev. 95, 749-784

Ke Y., Chang Y.Z., Duan X.L., Du J.R., Zhu L., Wang K., Yang X.D., Ho K.P. and Qian Z.M. (2005). Age-dependent and iron-independent expression of two mRNA isoforms of divalent metal transporter 1 in rat brain. Neurobiol. Aging 26, 739-748.

Lee J.Y., Cole T.B., Palmiter R.D., Suh S.W. and Koh J.Y. (2002). Contribution by synaptic zinc to the gender-disparate plaque formation in human Swedish mutant APP transgenic mice. Proc. Natl. Acad. Sci. USA 99, 7705-7710.

Lichten L.A. and Cousins R.J. (2009). Mammalian zinc transporters: nutritional and physiologic regulation. Annu. Rev. Nutr. 29, 153-176.

Liu S.T., Howlett G. and Barrow C.J. (1999). Histidine-13 is a crucial

residue in the zinc ion-induced aggregation of the A beta peptide of Alzheimer's disease. Biochemistry 38, 9373-9378.

Lovell M.A., Robertson J.D., Teesdale W.J., Campbell J.L. and Markesbery W.R. (1998). Copper, iron and zinc in Alzheimer's disease senile plaques. J. Neurol. Sci. 158, 47-52.

Lovell M.A., Smith J.L. and Markesbery W.R. (2006). Elevated zinc transporter-6 in mild cognitive impairment, Alzheimer disease, and pick disease. J. Neuropathol. Exp. Neurol. 65, 489-498.

Lovell M.A., Smith J.L., Xiong S. and Markesbery W.R. (2005). Alterations in zinc transporter protein-1 (ZnT-1) in the brain of subjects with mild cognitive impairment, early, and late-stage Alzheimer's disease. Neurotox Res. 7, 265-271.

Maynard C.J., Bush A.I., Masters C.L., Cappai R. and Li Q.X. (2005). Metals and amyloid-beta in Alzheimer's disease. Int. J. Exp. Pathol. 86(, 147-159.

Park I.H., Jung M.W., Mori H. and Mook-Jung I. (2001). Zinc enhances synthesis of presenilin 1 in mouse primary cortical culture. Biochem. Biophys. Res. Commun. 285, 680-688.

Ritchie C.W., Bush A.I., Mackinnon A., Macfarlane S., Mastwyk M., MacGregor L., Kiers L., Cherny R., Li Q.X., Tammer A., Carrington D., Mavros C., Volitakis I., Xilinas M., Ames D., Davis S., Beyreuther K., Tanzi R.E. and Masters C.L. (2003). Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch. Neurol. 60, 1685-1691.

Sensi S.L., Paoletti P., Bush A.I. and Sekler I. (2009). Zinc in the physiology and pathology of the CNS. Nat. Rev. Neurosci. 10, 780-791.

Sensi S.L., Ton-That D., Sullivan P.G., Jonas E.A., Gee KR., Kaczmarek L.K. and Weiss J.H. (2003). Modulation of mitochondrial function by endogenous Zn^{2+} pools. Proc. Natl. Acad. Sci. USA 100, 6157-6162.

Seubert P., Vigo-Pelfrey C., Esch F., Lee M., Dovey H., Davis D., Sinha S., Schlossmacher M., Whaley J., Swindlehurst C., Schiossmacher M., Whaley J., Swindlehurst C., Mccormack R., Wolfert R., Selkoe D., Lieberburg I. and Schenk D. (1992). Isolation and quantification of soluble Alzheimer's beta-peptide from biological fluids. Nature 359, 325-327.

Shoji M., Golde T.E., Ghiso J., Cheung T.T., Estus S., Shaffer L.M., Cai X.D., McKay D.M., Tintner R. and Frangione B. (1992). Production of the Alzheimer amyloid beta protein by normal proteolytic processing. Science 258, 126-129.

Stoltenberg M., Bruhn M., Søndergaard C., Doering P., West M.J., Larsen A., Troncoso J.C. and Danscher G. (2005). Immersion autometallographic tracing of zinc ions in Alzheimer beta-amyloid plaques. Histochem. Cell Biol. 123, 605-611.

Suh S.W., Jensen K.B., Jensen M.S., Silva D.S., Kesslak P.J., Danscher G. and Frederickson C.J. (2000). Histochemically-reactive zinc in amyloid plaques, angiopathy, and degenerating neurons of Alzheimer's diseased brains. Brain Res. 852, 274-278.

Sun X.Y., Wei Y.P., Xiong Y., Wang X.C., Xie A.J., Wang X.L., Yang Y.,

Wang Q., Lu Y.M., Liu R. and Wang J.Z. (2012). Synaptic released zinc promotes tau hyperphosphorylation by inhibition of protein phosphatase 2A (PP2A). J. Biol. Chem. 287, 11174-11182.

Takeda A. (2000). Movement of zinc and its functional significance in the brain. Brain Res. Rev. 34, 137-148.

Wang C.Y., Wang T., Zheng W., Zhao B.L., Danscher G., Chen Y.H. and Wang Z.Y. (2010). Zinc overload enhances APP cleavage and Aβ deposition in the Alzheimer mouse brain. PLoS One 5, e15349.

Wang C.Y., Xie J.W., Xu Y., Wang T., Cai J.H., Wang X., Zhao B.L., An L. and Wang Z.Y. (2013). Trientine reduces BACE1 activity and mitigates amyloidosis via the AGE/RAGE/NF-κB pathway in a transgenic mouse model of Alzheimer's disease. Antioxid. Redox Signal. 19, 2024-2039.

Wang T., Wang C.Y., Shan Z.Y., Teng W.P. and Wang Z.Y. (2012). Clioquinol reduces zinc accumulation in neuritic plaques and inhibits the amyloidogenic pathway in AβPP/PS1 transgenic mouse brain. J. Alzheimers Dis. 29, 549-559.

Wang Z.Y., Li J.Y., Danscher G. and Dahlström A. (2002). Localization of zinc-enriched neurons in the mouse peripheral sympathetic system. Brain Res. 928, 165-174.

Weiss J.H., Sensi S.L. and Koh J.Y. (2000). Zn^{2+}: a novel ionic mediator of neural injury in brain disease. Trends Pharmacol. Sci. 21, 395-401.

Xiong Y., Jing X.P., Zhou X.W., Wang X.L., Yang Y., Sun X.Y., Qiu M., Cao F.Y., Lu YM., Liu R. and Wang J.Z. (2013). Zinc induces protein phosphatase 2A inactivation and tau hyperphosphorylation through Src dependent PP2A (tyrosine 307) phosphorylation. Neurobiol. Aging 34, 745-756.

Xu H., Gao H.L., Zheng W., Xin N., Chi Z.H., Bai S.L. and Wang Z.Y. (2011). Lactational zinc deficiency-induced hippocampal neuronal apoptosis by a BDNF-independent TrkB signaling pathway. Hippocampus. 21, 495-501.

Zatta P., Drago D., Bolognin S. and Sensi S.L. (2009). Alzheimer's disease, metal ions and metal homeostatic therapy. Trends Pharmacol. Sci. 30, 346-355.

Zhang L.H., Wang X., Stoltenberg M., Danscher G., Huang L. and Wang Z.Y. (2008). Abundant expression of zinc transporters in the amyloid plaques of Alzheimer's disease brain. Brain Res. Bull. 77, 55-60.

Zhang L.H., Wang X., Zheng Z.H., Ren H., Stoltenberg M., Danscher G., Huang L., Rong M. and Wang Z.Y. (2010). Altered expression and distribution of zinc transporters in APP/PS1 transgenic mouse brain. Neurobiol. Aging. 31, 74-87.

Zheng W., Wang T., Yu D., Feng W.Y., Nie Y.X., Stoltenberg M., Danscher G. and Wang Z.Y. (2010). Elevation of zinc transporter ZnT3 protein in the cerebellar cortex of the AbetaPP/PS1 transgenic mouse. J. Alzheimers Dis. 20, 323-331.

Zheng W., Xin N., Chi Z.H., Zhao B.L., Zhang J., Li J.Y. and Wang Z.Y. (2009). Divalent metal transporter 1 is involved in amyloid precursor protein processing and Abeta generation. FASEB J. 23, 4207-4217.