Magnesium in Alzheimer's disease

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Abstract

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Alzheimer's disease (AD) is the most common form of dementia. It is characterized by a progressive cognitive impairment clinically, and excessive deposits of aggregated amyloid-β (Aβ) peptides pathologically. Environmental factors, including nutrition and metal elements, are implicated in the pathophysiology of AD. Magnesium (Mg) affects many biochemical mechanisms vital for neuronal properties and synaptic plasticity, including the response of N-methyl D-aspartate (NMDA) receptors to excitatory amino acids, stability and viscosity of the cell membrane, and antagonism of calcium. Mg levels were found to be decreased in various tissues of AD patients and negatively correlated with clinical deterioration. Moreover, Mg was demonstrated to modulate the trafficking and processing of amyloid-β precursor protein, which plays a central role in the pathogenesis of AD. Here, we review in vitro and in vivo data that indicated a role for magnesium in many biological and clinical aspects of AD.

Alzheimer's disease

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Alzheimer's disease (AD) is the most prevalent neurodegenerative disease in elderly people, affecting approximate 6-8% of all individuals over the age of 65 years. AD is characterized by progressive cognitive impairment and distinct neuropathological lesions in the brain, including intracellular neurofibrillary tangles, and extracellular, parenchymal and cerebrovascular senile plaques (Braak and Braak, 1991). Senile plaques are mainly constituted of a 39–42 amino acid peptide, amyloid-β protein (Aβ) (Glenner and Wong, 1984; Masters *et al.*, 1985), which is generally accepted as being neurotoxic and playing a central role in the pathogenesis of neuronal dysfunction and synaptic failure in Alzheimer's disease (Selkoe, 1991; Hardy and Selkoe, 2002). Aβ is derived from full-length amyloid-β precursor protein (APP) (Kang *et al.*, 1987; Qi-Takahara *et al.*, 2005), which is a type I trans-membrane protein composed of a large extracellular domain, a short transmembrane domain, and a cytoplasmic tail, by sequential proteolytic cleavages by β-secretase and γ-secretase. The β-cleavage of APP, catalysed by the well characterized transmembrane aspartyl protease β-site APP-cleaving enzyme (BACE) (Hussain *et al.*, 1999; Sinha *et*

al., 1999; Yan *et al.*, 1999; Haniu *et al.*, 2000), cleaves APP at the NH2- terminus of the Aβ sequence (Seubert *et al.*, 1993) to generates a soluble version of APP (sAPP) and a 99-residue COOH-terminal fragment (CTFβ or C99) which remains membrane bound.

C99 is further cleaved to release Aβ of varying lengths, predominantly Aβ40 and Aβ42 (Selkoe, 2001; Hussain *et al.*, 1999; Price *et al.*, 1998; Sinha *et al.*, 1999; Christensen *et al.*, 2004), by an atypical aspartyl protease, γ-secretase complex which contains at least four different proteins, namely Aph-1, nicastrin, presenilin, and Pen-2 (De Strooper, 2003; Edbauer *et al.*, 2003). Proteolysis by γ-secretase is heterogeneous; most of the full-length Aβ species produced is a 40- residue peptide (Aβ40), whereas a small proportion is a 42-residue COOH-terminal variant (Aβ42) (Esler and Wolfe, 2001). However, prior processing of APP by α-secretase precludes the formation of the neurotoxic Aβ. It cuts APP within the Aβ region (between residues Lys16 and Leu17 of Aβ), generating a sAPPα and a membrane- anchored 83-residue C-terminal fragment (CTFα or C83), which is also a substrate of γ-secretase (Esch *et al.*, 1990; Sisodia, 1992). α-Secretase is thought to be a metalloprotease, such as TNF-α converting enzyme (TACE) or a disintegrin and metalloprotease 10 (ADAM10) (Lammich *et al.*, 1999). Secreted APP exerts proliferative actions in a variety of cell types as well as neurotropic and neuroprotective effects (Mucke *et al.*, 1996).

Synaptic failure in AD is caused by accumulation and oligomerization of Aβ42 in limbic and association cortices (Selkoe, 2002). Mutations in the APP gene or presenilin (PS) 1 or 2 genes, which cause an autosomal dominant early onset familial AD (<5% of AD patients), increases the relative production of Aβ42 (Wiltfang *et al.*, 2001). In the majority of patients with so-called sporadic late-onset AD, an age-dependent accumulation of Aβ, caused by disturbed dynamic balance between anabolic and catabolic activities, has been implicated (Selkoe, 1999; 2001b). Also, environmental factors, such as metallic elements may play a protective or disruptive role in the pathogenesis of AD (for review, see Adlard and Bush, 2006; Shcherbatykh and Carpenter, 2007). Different metals may be involved in multiple aspects of the disease process, such as the regulation of APP gene expression and mRNA translation, the proteolytic processing of APP, the aggregation and degradation of Aβ, and the formation of neuro- fibrillary tangles. Heavy metals (e.g. lead, mercury and cadmium) are neurotoxic and associated with intellectual impairment (Bleecker *et al.*, 2005). Recent studies have implicated lead exposure in the subsequent elevation of APP and Aβ in animals (Basha *et al.*, 2005b) as well as in the aggregation of synthetic $A\beta_{1-40}$ in vitro (Basha *et al.*, 2005a). In the case of aluminium, another “toxic” metal, its relevance to AD is ascribed to the involvement in the formation of paired helical filaments (PHF), the

aggregation and toxicity of Aβ, and the generation of oxidative species (for review, see Gupta *et al.*, 2005). Transition metals (e.g. copper, zinc, and iron, which are essential in cell biology) can induce Aβ aggregation (Huang *et al.*, 2004; Mantyh *et al.*, 1993) and are found concentrated in and around the amyloid plaques in the AD brain (Lovell *et al.*, 1998). Disturbed homeostasis of these biometals in the AD brain (decreased copper levels, and increased concen- trations of iron, zinc, and manganese) has been reported (Cornett *et al.*, 1998; Deibel *et al.*, 1996). An imbalance of zinc and copper has been shown to significantly alter APP processing and Aβ generation in relevant animal models (Bayer *et al.*, 2003; Borchardt *et al.*, 1999; Phinney *et al.*, 2003; Sparks and Schreurs, 2003; Lee *et al.*, 2002; Friedlich *et al.*, 2004).

Neurological function of magnesium

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The magnesium ion, Mg^{2+}, is the second most abundant intracellular cation, serving to stabilize nucleic acid and protein structure (Subirana *et al.,* 2003; Brion and Westhof, 1997), and regulating over 300 enzymes as a cofactor (Romani *et al.,* 1992; 1993; Zhao *et al.*, 2002), including ATP- related enzymatic reactions (Hirata *et al.,* 2002; Ko *et al.*, 1999). Physiological concentrations of Mg are essential for synaptic conduction, and required for normal functioning of the nervous system. It has various effects at different concentrations on intellectual and neuronal functions via many bio-chemical mechanisms, including NMDA-receptor responses to excitatory amino acids and calcium influx (Nowak *et al.*, 1984; Mayer *et al.*, 1984; Vandenberg *et al.,* 1987; Matsuda *et al.*, 1987), inhibition of calcium channels (Iseri and French, 1984) and glutamate release (Lin *et al.*, 2002), effects on cell membrane fluidity and stability (Ebel and Gunther, 1980), and toxic effects of calcium (Alvarez-Leefmans *et al.*, 1987). These mechanisms have important roles in chronic neuronal degeneration and subsequent development of dementia.

The role of Mg in degenerative diseases has been the focus of increased attention in recent years. Continuous low Mg intake for two generations induces exclusive loss of dopaminergic neurons in rats (Oyanagi, 2005), and may support the Mg hypothesis in the pathogenesis of parkinsonism- dementia complex (PDC) of Guam. Mg supple- mentation prevents the loss of dopaminergic neurons and ameliorates neurite pathology in a PD model, indicating a role of Mg in protection of dopaminergic neurons in the substantia nigra from degeneration (Oyanagi *et al.*, 2006; Hashimoto *et al.*, 2008). Also, Mg at concentrations > 0.75 mM inhibits the aggregation of α-synuclein, induced either spontaneously or by incubation with iron (Golts *et al.*, 2002). Microinjection of magnesium into cells caused microtubule disassembly (Prescott *et al.*, 1988). Mg^{2+} and

Ca^{2+} effectively induced formation of approximately 340 kD aggregates of paired helical filament tau (PHF-tau) obtained from corticobasal degeneration (CBD) and AD but not normal tau proteins isolated from fetal and adult brains, as determined by sodium dodecyl sulphate (SDS)-polyacrylamide gel electrophoresis and immunoblotting (Yang *et al.,* 1999). This finding suggests regional elevation of these ions may trigger pathological deposition of PHF-tau in certain neurodegenerative disorders.

Magnesium in AD

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Recent evidence suggests that Mg was implicated in the pathogenesis of AD. Mg levels were decreased in the serum and brain tissues of AD patients in clinical, experimental and autopsy studies (Durlach, 1990; Glick, 1990a; Lemke, 1995; Andrási *et al.,* 2000; 2005; Vural *et al.,* 2010). Moreover, serum Mg levels in AD patients negatively correlated with the Global Deterioration Scale (GDS) and the Clinical Dementia Rating (CDR) (Cilliler *et al.,* 2007). A causal relationship between low Mg in hippocampal neurons and impairment of learning was also demonstrated in aged rats (Landfield *et al.,* 1984). Magnesium deficiency can lead to specific impairments in emotional memory (Bardgett *et al.,* 2005; Bardgett *et al.,* 2007), while magnesium therapy facilitates cognitive function recovery following brain injury; however, there are task and dose- dependent aspects to this recovery (Enomoto *et al.,* 2005; Hoane, 2005; Hoane, 2007). Increasing brain magnesium leads to the enhancement of both short-term synaptic facilitation and long- term potentiation and improves learning and memory functions in rats (Slutsky *et al.,* 2010). Interestingly, treatment of dementia patients with nutritional Mg support efficiently improved memory and other symptoms (Glick *et al.,* 1990b). However, therapeutic administration of Mg is still controversial regarding the treatment of AD, and high doses of Mg may have potential detrimental side effects (Clark and Brown, 1992; Fung *et al.,* 1995; Hallak, 1998; Ladner and Lee, 1999).

Neuronal degeneration occurs in PS1 mutant mice without extracellular Aβ deposits, suggesting it is caused by the accumulation of intracellular Aβ42 (Chui *et al.,* 1999). Deposits of intracellular Aβ42 are correlated with apoptotic cell death in AD brains (Chui *et al.,* 2001). The Aβ is derived from APP through sequential cleavages by β-and γ-secretases, whose enzymatic activities are tightly controlled by subcellular localization. Thus, delineation of how the intracellular trafficking of these secretases and APP are regulated is important for understanding AD pathogenesis. Although APP trafficking is regulated by multiple factors including PS1 (Cai *et al.,* 2003), a major component of the γ-secretase complex, and phospholipase D1, a phospholipid- modifying enzyme, APP can reciprocally

regulate PS1 trafficking. APP deficiency results in faster transport of PS1 from the trans-Golgi network to the cell surface and increased steady state levels of PS1 at the cell surface, which can be reversed by restoring APP levels (Liu *et al.*, 2009). However, it is not known whether altered magnesium level may also affect APP trafficking or/and processing. Recently, it has been demonstrated that magnesium modulated APP processing in a time- and dose-dependent manner: extracellular magnesium ($[Mg^{2+}]_o$) at high doses increased CTFα level and sAPPα release. In contrast, $[Mg^{2+}]_o$ at low doses enhanced CTFβ accumulation and Aβ secretion (Yu *et al.*, 2010). The mechanism of how varying magnesium concentrations led to shifts between α- and β-secretase cleavage of APP might be partially explained by the evidence that $[Mg^{2+}]_o$ at high doses promoted retention of APP on plasma membrane, whereas $[Mg^{2+}]_o$ at low doses reduced cell surface APP level (Yu *et al.*, 2010). All APP family members are predominantly cleaved in the late secretory pathway, including the plasma membrane and endosomes (Yamazaki *et al.*, 1996). Further, different secretase activities show distinct subcellular localization, namely α- secretase at the plasma membrane (Lammich *et al.*, 1999; Skovronsky *et al.*, 2000) and β/γ- secretases within endocytic compartments (Vassar *et al.*, 1999; Huse *et al.*, 2000 ; Cupers *et al.*, 2001 ; Kaether *et al.*, 2002; Ray *et al.*, 1999). Because targeting of APP to distinct subcellular compartments determines processing into amyloidogenic or non-amyloidogenic products, much attention has been focused on factors that regulate APP trafficking. Interestingly, several adaptor proteins are known to influence APP transport and processing. For example, F- spondin, a secreted factor that binds to the extracellular domain of APP (Ho and Sudhof, 2004), has been shown to increase levels of cell surface APP, promote α-cleavage of APP, and decrease β-cleavage of APP (Hoe *et al.*, 2005). Similarly, the extracellular matrix protein Reelin caused increased surface APP and a preference for α-cleavage over β-cleavage (Hoe *et al.,* 2006b). These findings suggest that trafficking and proteolysis of APP are regulated together. Thus a function of $[Mg^{2+}]_o$ in APP transport from/to the cell surface might be a possible explanation for its modulation of APP processing. In the light of Mg^{2+} as an antagonist of the NMDA receptor, our finding is corroborated by the previous report that chronic NMDA receptor activation decreased α-secretase-mediated APP processing and increased Aβ production in cultured cortical neurons (Lesne *et al.*, 2005). Furthermore, several lines of evidence suggest that APP metabolism and Aβ levels are closely correlated with neural activity in animals (Fazeli *et al.*, 1994; Turner *et al.*, 2004; Cirrito *et al.*, 2005; 2008) and humans (Buckner *et al.*, 2005). It has been demonstrated that decreasing neuronal activity by high $[Mg^{2+}]_o$ (10 mM $MgCl_2$) resulted in significant reduction of Aβ secretion, which may involve a change in

APP processing (Kamenetz *et al.*, 2003). However, the precise functional mechanism of how magnesium regulates APP transport and whether magnesium interacts with α- and β-secretase, or regulates enzyme activity, or their subcellular localization, remains undetermined but will be part of our future analysis.

The dose dependent response of sAPPα to increasing $[Mg^{2+}]_o$ implies high concentrations of Mg may exert protective effects against AD. Various studies have strongly established that secreted sAPPα possesses potent neurotrophic and neuroprotective activities against excitotoxic and oxidative insults (Mattson *et al.*, 1993; Schubert *et al.,* 1993), p53-mediated apoptosis (Xu *et al.*, 1999), and the proapoptotic action of mutant PS1 by activating the transcription factor NF-κB (Guo *et al.*, 1998). Moreover, sAPPα stimulates neurite outgrowth (Small *et al.*, 1994), regulates synaptogenesis (Morimoto *et al.*, 1998), exerts trophic effects on cerebral neurons in culture (Araki *et al.*, 1991), stabilizes neuronal calcium homeostasis and protects hippocampal and cortical neurons against the toxic effects of glutamate and Aβ peptides (Furukawa *et al.*, 1996). It also has been shown that intra- cerebroventricular administration of secreted forms of sAPPα to amnestic mice has potent memory-enhancing effects and blocks learning deficits induced by scopolamine (Meziane *et al.*, 1998).

Secreted Aβ increased upon low $[Mg^{2+}]_o$ (0.0 and 0.4 mM) compared with physiological concen- tration of Mg (i.e. 0.8 mM), whereas high $[Mg^{2+}]_o$ (1.2, 1.6, 4.0 mM) could not significantly lower total extracellular Aβ level (Yu *et al.*, 2010). The data are consistent with several reports showing a dissociation between sAPPα release and Aβ generation both in vitro or in vivo (Loefler and Huber, 1993; Querfurth *et al.,* 1994; Dyrks *et al.*, 1994; LeBlanc *et al.*, 1998; Rossner *et al.*, 2000), suggesting that there might be a more complex regulatory mechanism of these two processing events of APP. For instance, constitutive activation of PKC in guinea pig brain increased sAPPα secretion without any effect on secreted Aβ (Rossner *et al.*, 2000), suggesting that the α- and β-secretase pathways may be differentially controlled. Because Yu *et al.*, (2010) examined the effects of Mg only on the pathologically high production of Aβ, the modulation of the physiological Aβ production by Mg needs to be established in future studies. The steady-state level of Aβ peptide is determined by the rate of production from APP via β- and γ-secretases and degradation by the activity of several degradative enzymes, including neprilysin (Hama *et al.*, 2001; Iwata *et al.*, 2001; Shirotani *et al.*, 2001; Leissring *et al.*, 2003; Marr *et al.*, 2004; review see Wang *et al.*, 2006), insulin degrading enzyme (IDE) (Kurochkin *et al.,* 1994; Farris *et al.*, 2003), endothelin-converting enzyme (Eckman *et al.*, 2003) and MMPs (Roher *et al.*, 1994; Backstrom *et al.*, 1996; Leissring *et al.*, 2003).

Yu *et al.,* (unpublished data) also found that Mg deprivation resulted in a 50% decrease of neprilysin activity without alteration in the protein level of neprilysin and IDE. Thus, the exacerbated accumulation of Aβ induced by $[Mg^{2+}]_o$ at 0.0 mM resulted from both the enhanced production and aberrant catabolism.

Conclusion

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Magnesium participates in the biochemical mechanisms of neuronal properties and synaptic functions, which are involved in the patho- physiology of neurodegenerative diseases.

Magnesium was demonstrated to modulate APP trafficking and processing, and its level was found decreased in AD patients. Both clinical and experimental data implicated a role of Mg in the pathogenesis of AD. Given the prevalence of magnesium inadequacy in the general population (Ford and Mokdad, 2003), magnesium supplementation could constitute a potential novel pharmacological target for the treatment of AD via its action on APP processing.

Acknowledgement

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