Key minerals in neuropsychiatric disorders and mental ageing

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BRAINLABS

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Introduction

In 2004 the World Health Organization has estimated, that in high-income countries more than 25% of disease burden is formed by unipolar depressive disorders (8.2%), ischemic heart disease (6.3%), cerebrovascular disease (3.9%), Alzheimer and other dementias (3.6%) and alcohol use disorders (3.4%)(World Health Report, 2004). World-wide, estimates of disease burden appear to be different with relatively more emphasis on bacterial and viral infections. Better hygiene and medical care in high-income countries have undoubtedly increased life-expectancy, thereby shifting disease burden toward pathologies connected with an ageing population. However, other factors such as a different life style in high-income countries should also be taken into account, such as a preference for processed calorie-rich food with a low content of micronutrients, including electrolytes, minerals and vitamins (Popkin, 2006). Another confounding factor is the mineral content of our vegetables and fruits has been during the industrialization of our food-chain (NPK, mono cultures) which started after world war II. The complete removal of minerals from drinking water following distillation, desalination or reversed osmosis in some countries is another important factor.

Magnesium physiology and homeostasis

Magnesium is with potassium the most abundant cat-ion in living cells. It plays a fundamental role in a wide range of cellular events, biochemical reactions and physiological functions by activating over 325 enzyme systems, including those involved in ATP synthesis, carbohydrate metabolism, K^+ and Ca^{2+} transport, cell proliferation and membrane stability and function (Grubbs and Maguire, 1987; Saris et al., 2000; Wolf and Trapani, 2008; Barbagallo and Dominguez, 2010). Direct and indirect measurements indicate that total cellular Mg^{2+} content ranges between 17 to 20 mM in the majority of mammalian cell types examined (Romani and Scarpa, 1992; Wolf et al., 2003). However, the actual free Mg^{2+} concentration within cells is maintained between 0.5 and 1.0 mM, or less than 5% of the total cellular Mg^{2+} content in almost all cells examined, through the binding/buffering capacity of ATP, phospho-nucleotides, phospho-metabolites and possibly also proteins (Dai and Quamme, 1991; Romani and Scarpa, 1992, 2000). Indeed, magnesium ions have a crucial role in ATP synthesis through the oxidative phosphorylation/electron chain in mitochondria and by stabilizing the synthesized ATP through formation of the Mg-ATP^{2-} complex.

It has been proposed that the cytosolic Mg^{2+} concentration is a function of the energy charge of cells and that a defective mitochondrial respiration causes a derangement of cytosolic Mg^{2+} homeostasis. This is consistent with reports indicating mitochondria as the primary pool responsible for changes in cellular magnesium content, suggesting that mitochondria might act as magnesium stores (Kubota et al., 2005; Farruggia et al., 2006) and play a key role in regulating magnesium homeostasis (Murphy, 2000; Fatholahi et al., 2000). Because the electrochemical equilibrium potential for the cellular free Mg^{2+} concentration is approximately 50 mM in most mammalian cells under resting conditions (Flatman, 1984), it is evident that efficient mechanisms must operate in the cell membrane to maintain cytosolic free Mg^{2+} and total cellular Mg^{2+} content within the measured range. Examples are the magnesium channels TRPM7 (Nadler et al., 2001) primarily involved in Mg^{2+} homeostasis of individual cells and TRPM6 (Schlingmann et al., 2002), which given their preferential distribution in the kidneys and intestines are likely more involved in whole body homeostasis. While Mg^{2+} entry appears to be mediated by channels and channel-like mechanisms, Mg^{2+} extrusion is mediated by ion exchange mechanisms such as Na^{+}/Mg^{2+} exchange (Gunther et al., 1984) and possibly also H^{+}/Mg^{2+} exchange (Gunther and Vormann, 1990). Other mechanisms include carriers such as SLC41 (Wabakken et al., 2003), ACDP (Wang et al., 2003) and NIPA (Goytain et al., 2007, 2008).

Magnesium deficiency

Magnesium also acts as a voltage dependent antagonist and a noncompetitive inhibitor of N-methyl-D-aspartic acid (NMDA) receptors and ion channels including those for Ca^{2+} (see figure 1). Indeed, magnesium deficiency is associated with increased glutamate toxicity and Ca^{2+} entry in cells (e.g. Sapolski, 1992; Aarts and Tymianski, 2005). A diminished intracellular free Mg^{2+} concentration also reduces ATP synthesis and its utilization in the maintenance of ion gradients via the enzyme Na^{+}/K^{+}-ATPase (Grubbs and Maguire, 1987). Moreover, a reduced concentration of Mg^{2+} within cells impairs membrane stability through increased free radical production (Ebel and Gunther, 1980; Bara and Guiet-Bara, 1984). Thus important events associated with Mg^{2+} deficiency are the opening of Ca^{2+} channels, increased activation of postsynaptic NMDA receptors, increased membrane oxidation, but also increased release of neurotransmitters such as glutamate and neuropeptides such as substance-P (Tejero-Taldo et al., 2006; Kramer et al., 2009) and activation of the key inflammatory transcription factor $NF_{\kappa}B$ have been reported (Weglicki et al., 1994; Altura et al., 2003; Billard, 2006; Rayssiguier et al., 2010).

Glutamate excitotoxicity might mediate neuronal damage in neurodegenerative diseases (Lipton and Rosenberg, 1994; Rego and Oliveira, 2003). Intriguingly, the cat-ion channel TRPM7, which is crucial for Mg^{2+} homeostasis and cell survival (Schmitz et al., 2003), seems to be a critical mediator of anoxic cell death. TRPM7 gating appears to lie downstream of NMDA receptor mediated NO free-radical production. Accordingly, glutamate excitotoxicity would be the initial signal in a cell death cascade involving the production of peroxynitrite, which in turn activates TRPM7 channels. Calcium influx through TRPM7 channels then creates a positive feedback loop of reactive oxygen species (ROS) production, which eventually kills the cell (Aarts and Tymianski, 2005). Metabolic stress, with decreased levels of glucose, oxygen and other molecules and ions required for ATP production such as coenzyme Q10 and magnesium may also initiate neuronal apoptosis (Mattson, 2000). These stimuli are mostly involved in ageing and pathological conditions such as acute or chronic neurodegenerative diseases involving cell damage- triggered phosphorylation of p53 and transcription of pro-apoptotic factors leading to mitochondrial-dependent activation of caspase 9.

Magnesium might also play a role with blood brain barrier (BBB) integrity owing to its crucial role as cofactor in many enzymatic reactions in various cell types including endothelial cells of the BBB. Magnesium deficiency leads to or worsens a variety of central nervous system (CNS) pathologies by increasing inflammatory cytokines and reactive oxygen species and disturbing the activity of transporters in neurons, astrocytes, pericytes and capillary endothelial cells, which together constitute the neurovascular unit of the brain. However, information regarding the effects of magnesium on BBB integrity almost exclusively stems from studies in cerebrovascular diseases, such as traumatic brain injury, subarachnoid hemorrhage and stroke, and extrapolating the effects of magnesium in such conditions to neuropsychiatric disorders in the elderly is likely a bridge too far.

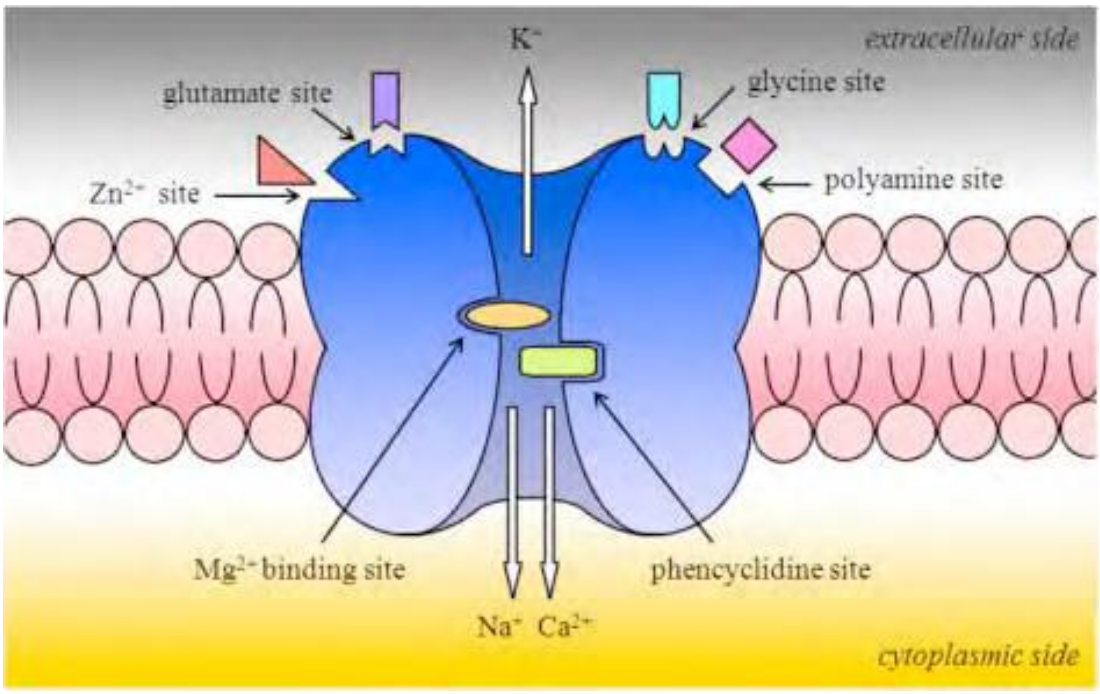

Figure 1: *Scheme of the NMDA receptor and its ligand binding sites The NMDA receptor is composed of four subunits (two NR1 and two NR2). NMDA receptor antagonists such as Mg^{2+} and phencyclidine (including ketamine, MK 801) block the ion channel, albeit at different positions.*

Serum concentration of Mg^{2+} in humans ranges between 1.7 and 2.3 mEq/L, but it might decrease during several pathological conditions (Romani and Scarpa, 2000; Musso, 2009). Serum Mg^{2+} and Ca^{2+} concentration is among other controlled by the parathyroid glands, releasing parathyroid hormone (PTH) and calcitonine to keep levels of both cat-ions within a narrow window, through various mechanisms involving bone cells, kidneys and intestines. Under normal physiological circumstances, magnesium influences PTH secretion in a manner similar to calcium by binding to the calcium sensing receptor on the parathyroid cell causing an increase in intracellular calcium and a subsequent decrease in PTH secretion. Conversely, with a fall in serum magnesium, serum levels of PTH increase.

During magnesium deficiency, however, there is impairment of PTH secretion. In addition to the disturbance in PTH secretion, serum concentrations of the active metabolite of vitamin D, 1,25(OH)2-vitamin D, are usually low in calcium and magnesium deficient patients. This may be secondary to a low serum PTH or renal resistance to PTH, as parathyroid hormone is a major physiological regulator of 1,25(OH)2-vitamin D synthesis. Magnesium deficiency may directly impair this process as 1,25(OH)2-

vitamin D synthesis is dependent on the presence of magnesium. As both PTH and 1,25(OH)2-vitamin D are the major regulators of bone and calcium homeostasis, magnesium deficiency may have an adverse effect on the skeleton. Indeed, the majority of research has been focused on the role of the calcium-PTH endocrine axis in osteoporosis (see e.g. Sahota et al., 1999, 2004, 2006; for review see Rude et al., 2009), especially in the elderly, but lately some attention has also been paid to the role of vitamin D and PTH in depressive disorders (Hoogendijk et al., 2008).

Because of its essential role in so many biochemical processes and its tight intra and extracellular regulation magnesium deficiency was for a long time not seriously considered to be a factor in human pathology, with the exception of rare cases involving highly penetrating mutations in genes coding for proteins directly responsible for Mg^{2+} homeostasis (e.g. TRPM7; Schlingmann et al., 2002). Yet evidence from epidemiological studies is accumulating that magnesium deficiency may indeed play a role in various cardiovascular and neuropsychiatric diseases, especially those connected with ageing. Many elderly suffer from mixed diseases of cardiovascular, diabetic and neuropsychiatric origin and often experience a loss of energy. The latter could be the common factor with a diminished availability of ATP in senescent cells, possibly pointing at an underlying intracellular magnesium deficiency. Indeed, reduction in brain extracellular free Mg^{2+} is associated with brain intracellular acidosis and a concomitant reduction of brain energy stores (Vink et al., 1988; Altura et al., 1995). A major problem encountered when testing this hypothesis is the assessment of magnesium deficiency. In the field of magnesium research there is now broad consensus that the only reliable way to assess magnesium deficiency is by estimating intracellular (cytosolic) Mg^{2+} levels through phosphorus magnetic resonance spectroscopy (^{31}P-MRS), wherein levels are indirectly measured through the chemical shift caused by binding of Mg^{2+} to phosphates, primarily ATP, phosphocreatine and inorganic phosphate (see figure 2), while using a calibration curve specifically developed for the *in vivo* assessment of the free Mg^{2+} concentration in human brain (Iotti et al., 1996). Other less complicated approaches such as measurement of Mg^{2+} serum or erythrocyte levels have proven less successful thus far (Yasmin I et al, 2010)

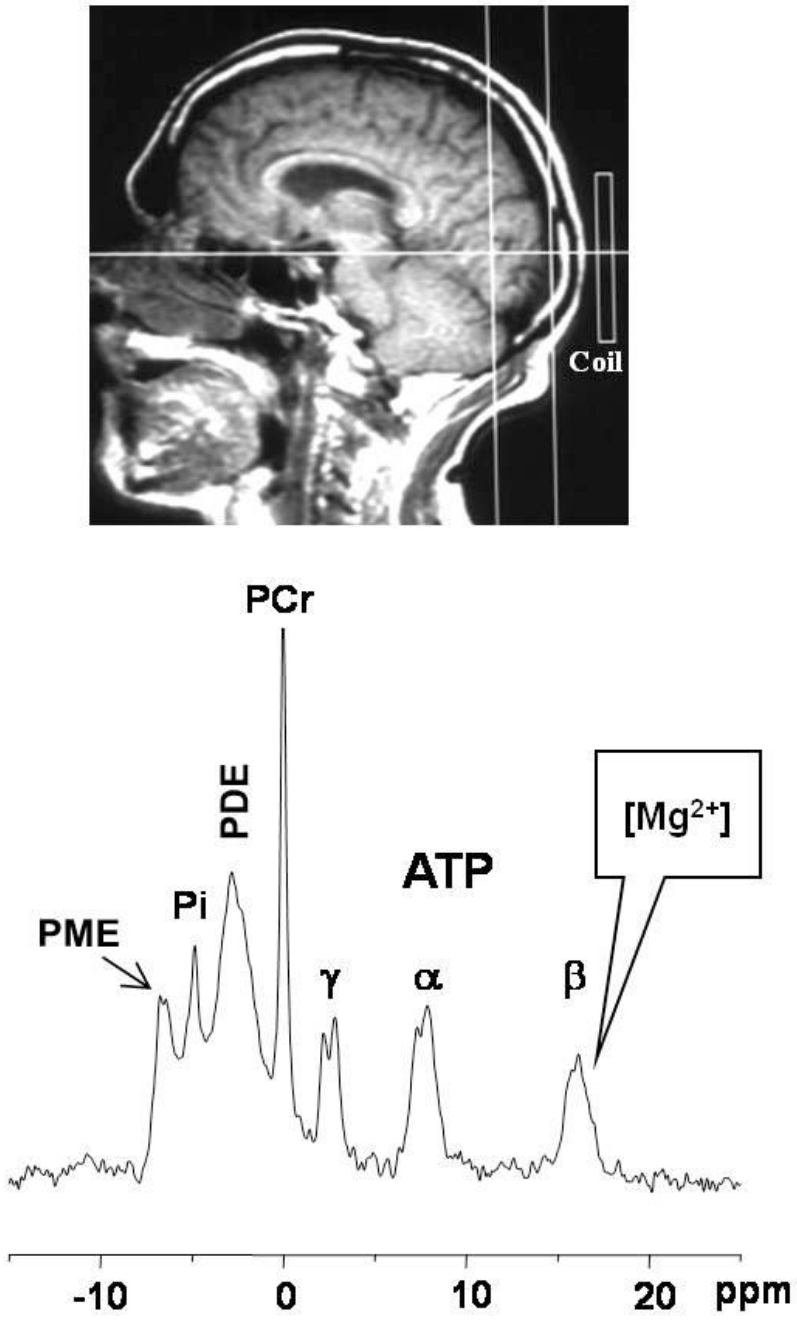

Figure 2: *Sagittal slice image of human brain acquired by magnetic resonance imaging, and ^{31}P-MRS spectrum acquired from occipital lobes placing the surface coil directly on the skull. Pi = inorganic phosphate; PCr = phosphocreatine; α,β,γ = ATP phosphoric groups; PME = phosphomonoesters; PDE = phosphodiesters; brain cytosolic [Mg^{2+}] is assessed from the chemical shift of β-ATP.*

Role of magnesium in unipolar depressive disorders

Depressive disorders cause 40% of all neuropsychiatric disorders (World Health Report, 2004). Besides core symptoms of depression, i.e. depressed mood and lack of energy, other symptoms may vary and include increased or decreased appetite and weight and sleep disturbances. Emotional reactivity can be very different with increases in sensitivity to social challenges, easy upset, sadness, but the opposite also occurs with an unresponsive mood leaving patients in a feeling-less state of mind. Feelings of guilt and sadness can be pronounced and may lead to suicidal ideation and finally suicide. A large proportion of the burden caused by depression is attributable to treatment-resistant depression (TRD), in many cases diagnosed following non-response to two different antidepressant treatments. Patients with TRD have a higher relapse rate and are more likely to suffer from comorbid physical and mental disorders frequently resulting in a marked and protracted functional impairment. With respect to a possible role of magnesium deficiency in MDD, increased aldosterone concentrations have been reported in patients with depression (Murck et al., 2002). It is important to note that administration of aldosterone increased urinary excretion of magnesium in humans (Horton and Biglieri, 1962). Yet regulation of whole body magnesium is far more complex than by aldosterone alone involving dynamic changes in mineralocorticoid receptor sensitivity, but also adrenergic mechanisms as witnessed for instance by the reduction of magnesium plasma levels in humans following acute β-adrenoceptor activation by adrenaline or salbutamol in humans (Whyte et al., 1987), indicating that stress is also an important factor. Moreover, magnesium regulates the function of the parathyroid glands, which in turn regulate magnesium levels and distribution (Zofkova and Kancheva, 1995). Yet it is clear that an inadequate central nervous system (CNS) Mg^{2+} concentration has a critical level below which neurological dysfunction occurs (Langly, 1991; Yasui et al., 1997). In contrast to peripheral changes in plasma and serum, changes within the CNS might be the true pointer for a magnesium deficiency. In subjects with MDD, a decrease in CSF magnesium concentration has been confirmed (Banki et al., 1985, 1986). A more recent study found an increased CSF Ca^{2+}/Mg^{2+} ratio in patients with MDD (Levine et al., 1999). Most recently, post mortem studies in patients with MDD showed a reduced magnesium concentration in brain tissue (Nowak et al., 2010). Importantly, human brain magnesium measurements using ^{31}P-MRS have demonstrated a reduced Mg^{2+} concentration in depressed patients, refractory to treatment with a selective serotonin reuptake inhibitor (Iosifescu et al., 2005). Several mechanisms have been proposed for a pathogenic role of magnesium deficiency in MDD centering on diminished NMDA receptor inhibition and increased stress sensitivity.

NMDA receptors

Magnesium depletion is specifically deleterious to neurons by causing NMDA-coupled Ca^{2+} channels to be biased toward opening (Sapolsky, 1992). At normal neuronal resting membrane potentials, pores of NMDA glutamate-gated ion channels are blocked by Mg^{2+} ions (Kandel et al., 1995; Bear et al., 2001; Mark et al., 2001; McMenimen, 2006)(see figure 1). In hippocampal synaptosomes, the Mg^{2+} blockade of the NMDA dependent ion channel is removed by the activation of protein kinase C (PKC) without changing membrane potential (Pittaluga et al., 2000). Deactivation of PKC by ATP depends on the presence of Mg^{2+} (Wolf et al., 1985) implying that magnesium deficiency might lead to a feed-forward cycle further releasing the Mg^{2+} blockade of the NMDA dependent ion current thereby increasing the influx of Ca^{2+} ions beyond manageable levels eventually leading to the generation of toxic reactive oxygen and nitric oxide species (Blaylock, 1999; Mark, 2001; Carafoli, 2005).

Studies on magnesium metabolism in affective disorders have not been consistent in the past and more recent studies form no exception (Barra et al., 2007; Eby and Eby, 2010; Lakhan et al., 2010; Singh et al., 2011; Camardese et al., 2012; Derom et al., 2012; Forsyth et al., 2012; Jacka et al., 2012). This might partly connect with the earlier discussed problems with the measurement of magnesium, and in case of magnesium supplementation also with differences in bioavailability. It is important to note that an early study in depressed patients has reported a decrease in total plasma magnesium but not ionized magnesium, with an increase in total magnesium following electroconvulsive shock therapy or tryptophan supplementation (Frizel et al., 1969). Interestingly, acute administration of the NMDA receptor antagonist ketamine has been reported to instantaneously reduce symptoms of depression (Berman et al., 2000; Zarate et al., 2006; Phelps et al., 2009; for review see Machado-Vieira et al., 2009). Conceivably, $GABA_A$ receptor agonists might also alleviate symptoms of depression (see figure 3). Yet, indirect $GABA_A$ agonists such as benzodiazepines have failed to demonstrate clinical efficacy in MDD (Feighner et al., 1990; Ansseau et al., 1991; Kennedy et al., 1991; Rickels et al., 1991). This might indicate that glutamate-GABA homeostasis is so profoundly disturbed in MDD, that only interventions directly targeted at the deranged glutamate neurotransmission are capable of restoring homeostasis and alleviating symptoms of depression. Following this line of thought one can speculate that if disturbances in GABA-glutamate homeostasis also occur in generalized anxiety disorders, they are probably less outspoken as suggested by the efficacy of benzodiazepines in anxiety.

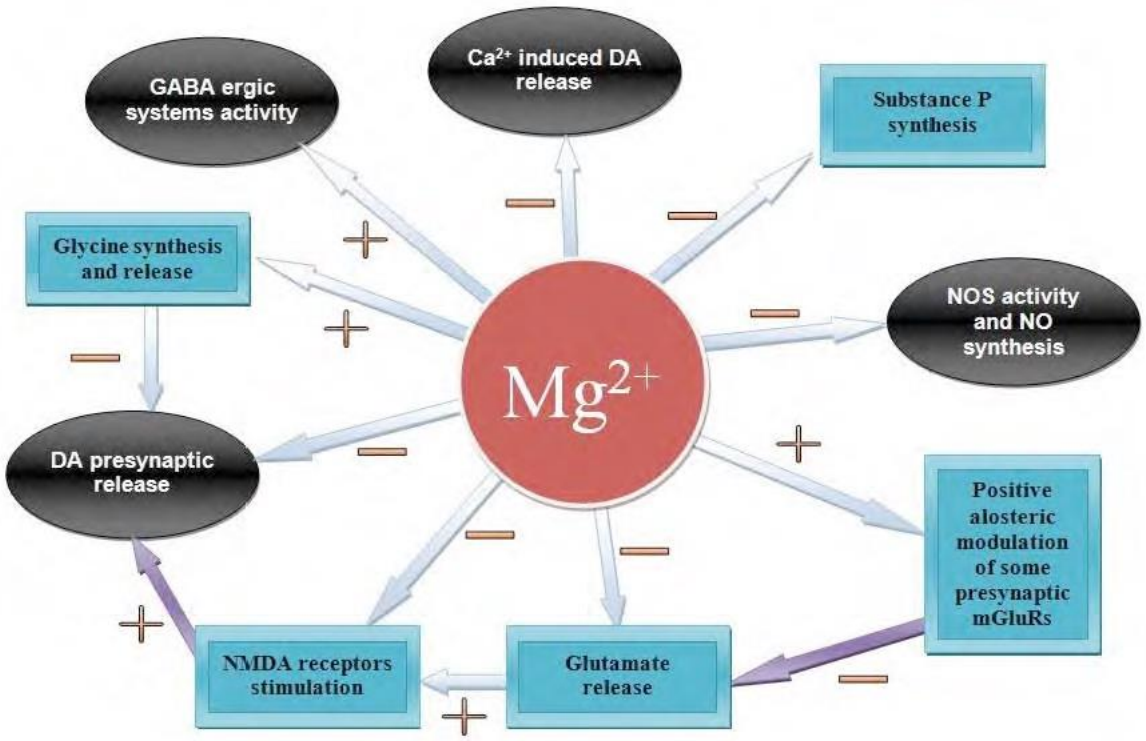

Figure 3: *Schematic depiction of Mg^{2+} interactions with glutamate, GABA, dopamine and substance P in opiate addiction. Take note that the inhibition of dopaminergic transmission by increased Mg^{2+}does not endorse pleasure per se.*

Stress sensitivity

Acute stress is associated with increased plasma magnesium levels and increased urinary magnesium excretion (Whyte et al., 1987; Murck, 2002). The shift of magnesium from the intracellular to the extracellular space by acute stress is thought to have a protective effect, but chronic stress may result in progressive intracellular magnesium deficiency with adverse effects on health (Seelig, 1994). Low Mg^{2+}/Ca^{2+} ratios augment the release of catechol amines in response to stress (Cadell et al., 1986; Seelig, 1994), and the fatty acids resulting from the increased β-adrenoceptor-induced lipolysis form poorly

dissociable complexes with magnesium ions, thus further reducing magnesium availability resulting in a vicious circle (Seelig, 1994). Magnesium deficiency also favors the release of vasoconstrictive and platelet aggregating factors thereby increasing the ratio of thromboxane B_2 and prostaglandinI_2 while enhancing intravascular blood coagulation (Ceremuzynski et al., 1978; Soma et al., 1988; Franz, 2004; Sontia and Touyz, 2007; Dong et al., 2008). Yet, magnesium deficiency may not induce specific pathology but instead reduce tolerance to secondary stress (Tejero-Taldo et al., 2006). Magnesium deficiency in mice showed increase anxiety related behavior and increased transcription of corticotropin- releasing factor (CRF) in the para-ventricular hypothalamic nucleus, and elevated adrenocorticotropic hormone (ACTH) plasma levels, pointing to an enhanced set point of the hypothalamic-pituitary-adrenal (HPA)-axis (Sartori et al., 2012). The mechanism is not exactly clear but may involve glutamate, angiotensin II, catechol amines, serotonin and estrogens. For example, Cratty and Birkle (1999) have shown that glutamate-stimulated release of CRF is antagonized by the addition of Mg^{2+} to cultured rat amygdala neurons. Magnesium stabilizes CRF receptor binding and is directly correlated to the number of CRF binding sites (Perrin et al., 1986). On the other hand Mg^{2+} stimulates Na^{+}/K^{+}-ATP-ase, which decreases CRF receptor sensitivity (De Sousa, 1995), indicating a complex regulation. Magnesium also decreases ACTH and modulates adrenocortical sensitivity for ACTH. Because intracerebroventricular administration of angiotensin II (ATII) increases the secretion of ACTH and arginine-vasopressin (AVP) through CRF stimulation, it is presumed that magnesium induces a suppression of HPA-axis activity, at least partly, through antagonism of ATII effects (Murck, 2002). Low blood magnesium levels have been associated with increased noradrenaline content in magnesium deficient mice (Amyard et al., 1995). It has also been reported that magnesium exerts a direct suppressant effect on noradrenergic locus coeruleus activity and that magnesium deficiency increases stress sensitivity (Henrotte et al., 1997). Magnesium also acts as a cofactor in serotonin synthesis, intervenes in serotonin receptor binding in vitro and exhibits a direct enhancing effect on 5-HT_{1A} receptor mediated neurotransmission (Mizoguchi et al., 2008; Szewczyk et al., 2008; Abaamrane et al., 2009). Serotonin is involved in neuroendocrine regulation of the HPA-axis through its actions on prolactin, oxytocin, AVP, CRF and ACTH activity (Jorgensen, 2007). HPA-axis dysregulation and sensitization of 5-HT_2 receptor mediated neurotransmission induced by CRF implicates chronic stress and serotonin in the etiology of depression (Szewczyk et al., 2008; Magalhaes et al., 2010). Finally because estrogens increase intracellular Mg^{2+} levels, magnesium deficiency could play a role in the increased HPA-axis responses to an emotional stressor in postmenopausal women (Dayas et al., 2000).

Clinical studies with magnesium supplementation

Notwithstanding the fact that TRD merits the central focus of medical research into MDD (Fekadu et al., 2009a,b,c), many patients who fulfill criteria of remission still have residual symptoms severe enough to interfere with quality of life (Nierenberg et al., 2010), indicating that more efficacious treatments with less side effects are also warranted for the latter group of patients. There are a number of open label studies on therapeutic effects of magnesium administration in major depressive disorder (MDD). The first but largely forgotten study was published in the first issue of the American Journal of Psychiatry, showing an 88% success rate of hypodermal magnesium sulfate administration in 50 patients with agitated depression (Weston, 1921-1922). Four case histories were presented showing rapid recovery (< 7 days) from MDD using 125-300 mg of magnesium (as glycinate and taurinate) with each meal and at bedtime (Eby and Eby, 2006). To date only one randomized, double blind controlled trial has compared the efficacy of oral magnesium administration with imipramine in the treatment of MDD. Twenty-three elderly patients with type II diabetes and magnesium deficiency were enrolled and randomly allocated to receive orally either 50 ml of a 5% $MgCl_2$ solution or 50 mg imipramine during 12 weeks. At the end of the treatment period, depression scores were identical between groups. However, serum magnesium levels were significantly higher in the $MgCl_2$ treatment group ($p<0.0005$) (Barragan-Rodriguez et al., 2008). A placebo controlled study in chronic fatigue syndrome, a disorder related to atypical depression, showed significant effects of intramuscular magnesium over placebo with respect to energy levels, pain and emotional reactions as measured by the Nottingham health profile score (Cox et al., 1991).

Role of magnesium in Alzheimer and other dementias

Alzheimer's disease (AD) is the prevalent neurodegenerative disease in elderly people, affecting 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 (Braak and Braak, 1991), including intracellular neurofibrillary tangles characterized by tau and phosho-tau protein accumulation and extracellular senile plaques, the latter mainly consisting of amyloid-β-protein (Aβ)(Glenner and Wong, 1984; Masters et al., 1985). Aβ is generally accepted as being neurotoxic and playing a central role in the pathogenesis of neuronal dysfunction and synaptic failure in AD (Selkoe, 1991; Hardy and Selkoe, 2002). Aβ is derived from the trans membrane full-length amyloid-β precursor protein (APP)(Kang et al., 1987; Qi-Takahara

et al., 2005) through sequential proteolytic cleavages by β-secretase and γ-secretase. The β-cleavage of APP by β-site APP cleaving enzyme (BACE)(Hussain et al., 1999; Sinha et al., 1999; Yan et al., 1999; Haniu et al., 2000) results in a soluble version of APP (sAPPβ) and a 99 amino acid fragment which remains membrane bound but is further cleaved to release Aβ of varying lengths (Price et al., 1998; Hussain et al., 1999; Selkoe, 2001) by a γ-secretase protein complex consisting of at least four different proteins, including presenilin-1 and Pen-2 (De Strooper, 2003; Edbauer et al., 2003). Recently it has been demonstrated that magnesium modulates APP processing in a time and dose dependent manner, with higher concentrations promoting retention of APP on the cell membrane (Yu et al., 2010). Through inhibition of the NMDA receptor, high concentrations of magnesium may also stimulate α-secretase-mediated APP processing at the expense of β processing, thus decreasing Aβ production (Lesne et al., 2005). Moreover, the secreted soluble form of APP following α-cleavage (sAPPα) may possess strong 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 pro-apoptotic action of mutant presenilin-1 by activating the transcription factor NFκB (Guo et al., 1998). Moreover, sAPPα stimulates neurite outgrowth (Small et al., 1994), regulates synaptogenesis (Morimoto et al., 1998), exerts trophic effects (Araki et al., 1991), stabilizes neuronal calcium homeostasis and protects hippocampal and cortical neurons against the toxic effects of glutamate and Aβ fragments (Furukawa et al., 1996). Soluble APPα may also have memory enhancing effects and block scopolamine induced learning deficits (Meziane et al., 1998). Given the prevalence of magnesium deficiency in the general population (Ford and Mokdad, 2003), magnesium supplementation might have potential in the prevention and treatment of dementia including AD through its action on APP processing.

Clinical studies with magnesium supplementation

Although clinical trials with magnesium supplementation in dementia could not be found, very recently the Japanese Hisayama Study concluded that higher self-reported dietary intakes of potassium, calcium, and magnesium reduce the risk of all-cause dementia, especially vascular dementia, in the general Japanese population (Ozawa et al., 2012).

Role of magnesium in normal ageing

In addition to the involvement of magnesium deficiency in neurodegenerative diseases (Basun et al., 1991; Andrasi et al., 2000, 2005) it may also play a role with normal cognitive ageing as witnessed by animal studies wherein decreased Mg^{2+} levels impair memory functions (Bardgett et al., 2005, 2007) while chronically elevating plasma Mg^{2+} over several days improves reversal learning in the hippocampus-dependent T-mase task (Landfield and Morgan, 1984). However, whether brain Mg^{2+} levels are really altered in these studies has been questioned considering that Mg^{2+} loading into the brain is tightly regulated by active transport processes that maintain a concentration gradient between CSF and plasma. In fact, a long-lasting increase in plasma Mg^{2+} levels following intravenous injection of $MgSO_4$ had little effect on brain levels both in animals and humans (Kim et al., 1996; McKee et al., 2005). This rigorous control of brain Mg^{2+} levels has apparently been overruled by administration of the highly bioavailable Mg^{2+}-L-threonine compound in rats, which increased CSF Mg^{2+} concentrations by at least 15 % (Slutsky et al., 2010). The increase of CSF magnesium was associated with significant improvements of learning abilities, working memory as well as short and long term memory compared to control animals (Slutsky et al., 2010). The underlying mechanism is unlikely to involve a change in Mg^{2+} blockade of the NMDA receptor (Potier et al., 2000) but rather Mg^{2+} mediated increased synthesis of the co-agonist D-serine (Junjaud et al., 2006; Mothet et al., 2006; Turpin et al., 2009; Potier et al., 2010). Another proposed mechanism is through alteration of cholinergic neurotransmission. Although direct evidence is still lacking, several literature data argue for the possibility that changes in brain Mg^{2+} may contribute to the age-associated impairment of acetylcholine dependent synaptic activity. For instance, hypomagnesia significantly weakened responses of cortical neurons to iontophoretically applied acetylcholine (El-Beheiry and Pull, 1990) while high affinity binding at the muscarinic receptor in AD is closely regulated by Mg^{2+} (Ladner and Lee, 1999). A placebo-controlled, randomized cross-over study suggests that oral Mg^{2+} administration partially reverses sleep EEG and nocturnal neuroendocrine changes occurring during aging (Held et al., 2002). Notably, the WHO reached consensus that in a majority of the world's population, the dietary Mg^{2+} intake is lower than recommended, especially in the ageing population (Galan, 1997; Ford and Mokdad, 2003).

Magnesium supplementation

Because magnesium supplementation is relatively cheap and have little unwanted side effects it would be an ideal choice to prevent and treat diseases related to ageing. However, there are still issues to be resolved regarding the bioavailability of magnesium. Several studies have been performed with oral administration of magnesiumoxide and salts such as magnesium chloride, magnesium sulfate indicating only modest bio-availability. Studies have been performed with chelated magnesium in the form of Mg-L-threonine (Slutsky et al., 2010) and Mg-biglycinate (Eby and Eby, 2006) indicating substantially improved bioavailability. An explanation may be found in the notion that free Mg^{2+} competes with other minerals like Ca^{2+} for absorption in the intestines, while chelated minerals do not. This is also supported by the minimal incidence of diarrhea with the chelated formulations.

Red blood cells with low glutathione peroxidase activity are known to inhibit cellular magnesium entry (Howard JM, 1994). Oxydative stress causes glutathione depletion, hence when cells are exposed to oxydative stress, selenium facilitates magnesium enterance in : 1) erythrocytes, 2) liver, kidney, heart and spleen tissue (Nawarath et. Al; 1995).

Biological function of zink

Zinc is a trace element, essential for living organisms. In humans, zinc plays "ubiquitous biological roles" (Hambidge and Krebs, 2007). More than 300 enzymes require zinc for their activities. It plays an important role in DNA replication, transcription, gene expression, signal transduction and protein synthesis, influencing cell division and differentiation (Frederickson, 1989). In the brain, zinc is stored in specific synaptic vesicles by glutamatergic neurons (Bitanihirwe and Cunningham, 2009) and can "modulate brain excitability" (Hambidge and Krebs, 2007). It has a key role in synaptic plasticity and thus in learning (Nakashima and Dyck, 2009). The highest amount of zinc is present in the brain, especially in the hippocampus, amygdala and neocortex (Frederickson, 1989; Frederickson et al., 2000; Vallee and Falchuk, 1993). Neurons with terminals containing zinc ions are called zinc enriched (ZEN) neurons (Frederickson et al., 2000; Wang et al., 2001). ZEN neurons in cortex, amygdala and hippocampus are most likely glutamatergic (Frederickson and Moncrieff, 1994). The majority of spinal cord zinc-enriched terminals are GABA-ergic and the other ones are glycinergic (Wang et al., 2001). The transport of zinc into the brain occurs via the brain barrier system: the blood-

brain and blood-cerebrospinal fluid barriers (Takeda and Tamano, 2009). Cellular zinc homeostasis is in part regulated by specific zinc transporters belonging to two gene families: the ZnT proteins [solute-linked carrier 30 (SLC30)] and the Zip (Zrtand Irt-like proteins) family [solute-linked carrier 39 (SLC39)] (Liuzzi and Cousins, 2004). In physiological concentrations zinc displays neuro-protective activity, although high concentrations of zinc are neurotoxic (Bancila et al., 2004; Cote et al., 2005). There have been several reports demonstrating the critical role of zinc ion availability in memory function, behavior, learning, neurogenesis, processes related to brain aging and neurological diseases (Mocchegiani et al., 2005; Bitanihirwe and Cunningham, 2009; Sensi et al., 2009; Suh et al., 2009; Takeda, 2000;Takeda and Tamano, 2009).

Role of zinc in depression

Over the last ten years, considerable evidence has been gathered suggesting a link between zinc and depression. One of the major hypotheses of major depression is based on altered neurotransmission in monoaminergic and recently also in amino- acidergic systems (Pilcet al., 2002; Skolnick et al., 2001). Moreover, recent data indicate that alterations in zinc (a natural modulator of amino-acidergic neurotransmission) homeostasis may contribute to mood disorders and may be involved in antidepressant-like actions in laboratory models (Nowak and Szewczyk, 2002). It has been reported that serum zinc levels are particularly low in treatment resistant major depressives (Maes et al., 1997) and that serum zinc levels normalize with successful antidepressant treatment (Maes et al., 1997; Schlegel-Zawadzka et al., 2000). One of the first studies indicated that depressed patients exhibit a significantly lower serum zinc level than psychiatrically normal controls (McLoughlin and Hodge, 1990; Maes et al., 1994; Nowak et al., 1999). Moreover, negative correlation between serum zinc concentration and the severity of depression was found (Maes et al., 1994; Nowak et al., 1999). A preliminary study performed in pregnant women indicated that a lower serum zinc concentration may also accompany antepartum and postpartum depressive symptoms (Wojcik et al., 2006). Also, in this study the serum zinc level was negatively correlated with the severity of the depressive symptoms. Further support of the hypothesis that zinc concentration might be a sensitive and specific marker of depression comes from the findings that the lower serum zinc level may be normalized after successful antidepressant therapy (Maes et al., 1997; McLoughlin and Hodge, 1990; Schlegel-Zawadzka et al., 2000). The stress associated hormones epinephrine and glucocorticoids increase liver metallothionein (MT) and reduce serum zinc (Cousins et

al., 1986). Thus, this could indeed be part of the mechanisms where by depressed individuals have reduced serum zinc levels. According to a review by Leonard and Maes (2012) activation of oxidative and nitrosative pathways may contribute to depression, causing damage to DNA, mitochondria, proteins, functional intracellular signaling molecules involved in the pathophysiology of depression. Chronic zinc deprivation may result in an increased sensitivity to oxygen and nitric oxide species, while its administration increases the antioxidant capacity. Recent data also points to the involvement of zinc – a modulator of glutamatergic neurotransmission – in mood disorders and in the mechanism(s) of antidepressant activity (Nowak et al., 2005; Szewczyk et al., 2008; 2010). Preclinical studies have demonstrated the antidepressant-like activity of zinc in animal tests and models (Cieslik et al., 2007; Kroczka et al., 2000, 2001; Nowak et al., 2003; Rosa et al., 2003; Sowa-Kucma et al., 2008). Moreover, zinc has been shown to enhance the activity of antidepressant drugs (Cieslik et al., 2007; Cunha et al., 2008; Kroczka et al., 2001; Szewczyk et al., 2002, 2009), while zinc deficiency produced depressive-like alterations in behavioral and neurochemical studies (Corniola et al., 2008; Takeda and Tamano, 2009; Tassabehji et al., 2008; Whittle et al., 2009).

NMDA receptors

Synaptic zinc is involved in the modulation of glutamate receptors such as N-methyl-D-aspartate (NMDA); α-amino-3-hydroxy-5-methyl- 4isoxazole-propionic acid (AMPA), glutamate metabotropic receptors (mGluR) as well as γ-aminobutyric acid (GABA) receptors and probably also in glycinergic transmission (Smart et al., 2004; Mocchegiani et al., 2005; Takeda and Tamano, 2009). The best characterized target for synaptic zinc is the NMDA receptor complex. Two different mechanisms of action for zinc on the NMDA receptor channel complex were identified: a voltage-independent, non-competitive (allosteric) inhibition, responsible for reducing the channel-opening frequency, and voltage-dependent inhibition, representing an open channel blocking effect of zinc (Christine and Choi, 1990; Paoletti et al., 2009).

Zinc also modulates the AMPA glutamate receptors, although at these particular receptors zinc acts as an enhancer and the presence of the GluR3 subunit seems to be necessary for the modulation of zinc (Paoletti et al., 2009). Zinc also has the potential to influence GABAergic neurotransmission through the modulation of pre-synaptic transmitter release and interaction with the $GABA_A$ receptor (Smart et al., 2004). This $GABA_A$ receptor inhibition is subtype-specific,

and a more likely target for zinc modulation are receptors that lack γ subunits such as αβ or αβδ receptors (Smart et al., 2004).

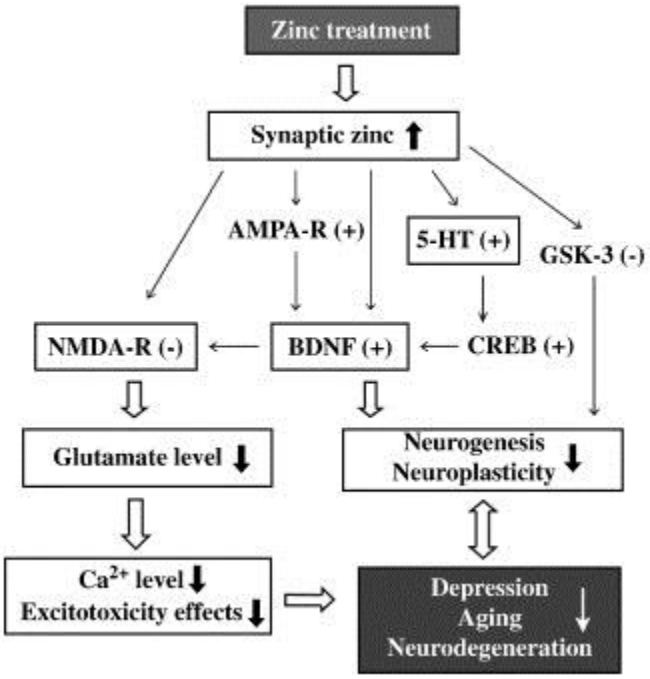

Fig. 1. Possible mechanisms of the antidepressant action of zinc treatment and zinc regulation of depression, aging and neurodegeneration. Three main targets of antidepressant treatment: NMDA, BDNF and 5-HT seem to be involved in the antidepressant action of zinc. Zinc treatment inhibits the function of the NMDA receptor and enhances the activity of BDNF directly or through the 5-HT/CREB pathwayor potentiation of AMPA receptor activity, which in turn leads to the inhibition of NMDA receptor function and a decreased glutamate level. This inhibitory modulation of glutamate signaling by zinc can prevent or attenuate the depression or age-related impairments, attenuate neurogenerative processes and enhance neurogenesis or neuronal plasticity. (+) indicates increased activation or production; (−) indicates decreased activation or production.
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Clinical studies with zink supplementation

Clinical studies have indicated the reduction of the blood zinc level in depressed patients (Amani et al., 2010; Maes et al., 1994, 1997; McLoughlin and Hodge, 1990; Nowak et al., 1999. Human trials designed to test the efficacy of zinc as an adjunct to antidepressant drug therapy have been consistent with the

findings in rodents. In a double-blind trial, 20 patients diagnosed with major depression using *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) criteria were given oral zinc supplementation (25 mg/d) or a placebo in addition to standard antidepressant drug therapy. Patients were assessed before zinc treatment and at 2, 6, and 12 weeks using the HDRS and the Beck Depression Inventory. These measures of depression status showed that 6 weeks of zinc supplementation augmented antidepressant drug therapy by over 50%. This difference was not only statistically significant, but was sustained through the full 12 weeks of the study (Nowak et al., 2003). Another clinical study demonstrated that zinc enhanced antidepressant efficacy in, especially, treatment-resistant patients suffering from major depression (Siwek et al., 2009). Several clinical studies showed better response to common antidepressants, when supplemented with zinc (Siwek et al., 2009; 2010). The clinical efficacy of zinc in the treatment of depression may in part be explained by its anti-oxidant properties (Leonard and Maes, 2012). According to Leonard and Maes (2012) activation of oxidative and nitrosative pathways may contribute to depression, causing damage to DNA, mitochondria, proteins, functional intracellular signaling molecules involved in the pathophysiology of depression. Chronic zinc deprivation may result in an increased sensitivity to oxygen and nitric oxide species, while its administration increases the antioxidant capacity. Recently a study has been performed to examine whether Zn supplementation improves mood states in young women using a double-blind, randomized and placebo-controlled procedure. The major outcome measures were psychological assessments, somatic symptoms and serum Zn. Thirty women were placed randomly and in equal numbers into two groups, and they ingested one capsule containing multivitamins (MVs) or MV and 7 mg Zn daily for 10 weeks. Women who took MV and Zn showed a significant reduction in anger-hostility score (P=0.009) and depression-dejection score (P=0.011) in the Profile of Moods State (POMS) and a significant increase in serum Zn concentration (P=0.008), whereas women who took only MV did not. The results suggest that Zn supplementation may be effective in reducing anger and depression (Sawada and Yokoi, 2010).

Zinc status is inversely related to anxiety in animals and young children (Takeda et al., 2007; Hubbs-Tait et al., 2007). DiGirolamo et al. (2010) studied school-age children in Guatemala, a population at risk for zinc deficiency, to assess the effects of zinc supplementation on mental health. Six months of zinc supplementation increased serum zinc concentrations, which were inversely associated with decreases in depressive symptoms (estimate: -0.01 points per µg Zn/dL; P = 0.01), anxiety (estimate: -0.012 points per µg Zn/dL; P = 0.02), internalizing symptoms (estimate: -0.021 points per µg Zn/dL; P = 0.02), and social skills (estimate: -0.019 points per µg Zn/dL; P = 0.01).

The results of Siwek et al., 2009 demonstrate that the addition of zinc hydroaspartate supplements to conventional antidepressant pharmacotherapy such as imipramine improves both the efficacy of antidepressant response as well as the speed of onset of therapeutic effects. Moreover, this effect is almost entirely due to the effect of zinc hydroaspartate supplementation in previous antidepressant nonresponders. Although beneficial effects of zinc supplementation on antidepressant response were suggested by an earlier pilot study of Nowak et al. (2003), the study of Siwek et al (2009) represents the first large scale clinical trial of zinc augmentation therapy. The authors concluded that zinc supplementation augments the efficacy and rate of onset of therapeutic response to imipramine treatment, particularly in patients previously nonresponsive to antidepressant pharmacotherapies. Moreover this study has provided the necessary clinical population to separately assess the effects of zinc supplementation in antidepressant responsive and nonresponsive populations. Finally, these data indicate that the combination of imipramine with zinc is safe and well-tolerated. It is possible that zinc supplementation may augment inhibition of pathologically hyper-active NMDA receptors in non-responder patients.

Role of zinc neurodegeneration and dementias

Zinc homeostasis and metabolism have been suggested to play a major role in many processes related to brain aging and in the onset and development of age-related neurodegenerative diseases (Doraiswamy and Finefrock, 2004, Mocchegiani et al., 2001 and Huang et al., 1997). In fact, zinc acts as neuromodulator at excitatory synapses and has a considerable role in the response to stress, in the process of myelination and in the functionality of zinc-related proteins contributing, as such, to maintaining brain compensatory capacity (Takeda, 2000). Alterations in zinc homeostasis have been reported in Parkinson's and Alzheimer's disease as well as in transient forebrain ischemia, seizures and traumatic brain injury, but little is known regarding the ageing brain. There is much evidence that that age-related changes, frequently associated to a decline in brain functions and impaired cognitive performances, could be related to dysfunctions affecting the intracellular availability of zinc ions.

Physiological supplementation with zinc improves and restores the deranged immune-endocrine functions in ageing, prolongs the life of old mice and enhances the resistance to infections in HIV patients, in Down's syndrome subjects and in the elderly (Mocchegiani et al., 2004). The beneficial effect

of zinc supplementation for brain function is controversial in zinc deficiency, aging and age-related neurodegenerative diseases.

Literature data from experimental animals suggest that deranged zinc homeostasis may occur in ageing associated to a decline in brain functions. One of the causes may be an altered homeostasis of MT and other zinc-binding proteins, such as alpha2 macroglobulin (A2M), which protect against stress and inflammation during young/adult age but turn into being harmful with ageing. In fact, despite total brain zinc content is unchanged in the brain of aged animals compared to the young/adult, the activity of some zinc dependent enzymes is impaired and large amounts of zinc have been found in the core of Alzheimer's disease senile plaques. The role played by MT and A2M is reported in ageing and Alzheimer's disease and on some polymorphisms of A2M and inflammatory genes (cytokines and their receptors) because some of them may be affected by zinc, via MT homeostasis (Moncchegiani and Malavolta, 2007).

Zinc deficiency is common in normal elderly individuals (Prasad et al., 1993). The lower concentration of serum Zn observed in patients with AD confirms the results of several previous studies (Brewer et al., 2010; Dong et al., 2008). Zinc deficiency has been linked to dementia (Burnet, 1981), and the progression of other age-related diseases, such as atherosclerosis, diabetes type 2, and cancer. The reduced concentration of serum Zn in patients with AD may result from Zn binding to Aβ and/or amyloid precursor proteins in the brains thus sequestering it from serum. Alternatively, the decreased serum Zn concentration may be associated with decreased brain ZnT-1 expression and subsequent alterations in cellular Zn distribution thus in turn contributing to AD progression by increasing Aβ processing and deposition (Dong et al., 2008). A phase II study of the Cu/Zn ionophore PBT2 reported improved cognition in patients with AD (Faux et al., 2010) suggesting that chronic Zn deficiency may contribute to the progression of AD-related cognitive dysfunction.

Several lines of evidence (reviewed in Corona et al., 2011) now indicate that altered levels of zinc (Zn^{2+}) in the brain could contribute to formation of the two major neuropathological hallmarks of Alzheimer's disease (AD): amyloid plaques and neurofibrillary tangles. Amyloid-β peptides in a soluble oligomeric form, or in the aggregated form found in cortical amyloid plaques, are heavily implicated in the pathogenesis of AD (Hardy, 2009) and Aβ aggregation is accelerated by Zn^{2+} *in vitro* (Bush et al., 1994; Ha et al., 2007; Noy et al., 2008). Altered synaptic Zn^{2+} levels affect Aβ aggregation *in vivo* (Lee et al., 2002). Zn^{2+} co-localizes with amyloid plaques and congophilic vessels in AD brain tissue (Suh et al., 2000; Miller et al., 2006; Zhang et al., 2008). Altered Zn^{2+} levels can also affect tau protein phosphorylation and

aggregation, which underlies the formation of neurofibrillary tangles in AD (Mo et al., 2009). Increased total Zn^{2+} levels have been detected in AD postmortem brain compared to controls, with the increase correlating with advancing AD pathology (Deibel et al., 1996; Danscheret al., 1997; Religa et al., 2006). Zinc binds to tubulin and affects its polymerization into microtubule-associated proteins MTs (Frederickson, 1989; Adlard and Bush, 2007). Zinc deficiency may also lower levels of α- and β-tubulin, MAP2 expression and impair microtubules MT polymerization (Wang et al., 1999; 2000). Zinc deficiency effects on lowered MT polymerization rates are apparently mediated through decreased electrostatic attraction between tubulin dimers, as well as decreased expression of MAP-tau, MAP2, and potential lowering of MAP-tau binding to MTs. It has been proposed, that based on β-amyloid-induced alterations in zinc ion concentration inside neurons affecting stability of polymerized microtubules, their binding to MAP-tau, and molecular dynamics involved in cognition. Zn also may play a role in multiple pathways relevant to AD, in particular with the processing of A*β*PP and aggregation of A*β*. A*β*PP synthesis is regulated by Zn-containing transcription factors (NF-*κ*B and sp1) and although Zn is essential for their activity (Yang et al., 1995; Zabel et al., 1991; Zeng et al., 1991) it is unclear whether the activity *in vivo* is regulated by Zn availability. In addition to the potential influence of Zn on A*β*PP expression, it also influences processing of the protein. Normal processing of A*β*PP by *α*-secretase cleavage in the Golgi complex leads to formation of sA*β*PP, a neurotrophic factor (Wilquet and De Strooper, 2004). Additional proteolytic processing of A*β*PP by *β*-secretase (BACE) at the *β*-cleavage site (Hussain et al., 1999., Andrasi et al., 2000; Sinha et al., 1999; Vassar et al., 1999; Calingasan et al., 1999) occurs in endosomes (Kinoshita et al., 2003; Koo et al., 1994)] at the lower pH conditions necessary for *β*- secretase activity (Wilquet and De Strooper, 2004). Further processing by the *γ*-secretase complex at the plasma membrane (reviewed in (Wilquet and De Strooper, 2004) leads to formation of A*β*, a 40 or 42 amino acid peptide that is the major component of senile plaques (SP) in AD (Sisodia and St George-Hyslop, 2002). Additionally, A*β*PP contains a ligand-binding site for Zn, and it is tempting to hypothesize that low extra-parenchymal Zn early in disease progression may lead to increased levels of brain Zn. These elevations of Zn could then become concentrated in subcellular organelles in which A*β* processing occurs, leading to increased generation of oligomeric A*β* species and the promotion of oxidative damage associated with AD. As the disease progresses and extra-parenchymal Zn levels normalize, the resulting alterations in multiple ZnT proteins could further promote A*β* aggregation and SP formation

To evaluate zinc status in Alzheimer's disease and Parkinson's disease, 29 patients with Alzheimer's disease, 30 patients with Parkinson's disease, and 29 age- and sex-matched controls were studied. All patients and controls were older than 50 years of age, and all zinc and copper supplements were

prohibited beginning 30 days prior to study. Blood zinc and urine zinc were measured. Results showed a significantly lower blood zinc concentration in patients with Alzheimer's and patients with Parkinson's than in controls. These patients are probably zinc deficient because of nutritional inadequacy. It is quite possible that zinc adequacy is important in neuronal health, and that zinc therapy would be therapeutically useful in AD and PD in correcting zinc inadequacy (Brewer et al., 2010).The overall effect of brain zinc (Zn^{2+}) in the progression and development of Alzheimer's disease (AD) is still not completely understood. Although an excess of Zn^{2+} can exacerbate the pathological features of AD, a deficit of Zn^{2+} intake has also been shown to increase the volume of amyloid plaques in AD transgenic mice (Corona et al., 2010). The investigators found that Zn^{2+} supplementation greatly delays hippocampal-dependent memory deficits and strongly reduces both Aβ and tau pathology in the hippocampus. They also evaluated signs of mitochondrial dysfunction and found that Zn^{2+} supplementation prevents the age-dependent respiratory deficits observed in untreated 3xTg-AD mice. They also found that Zn^{2+} supplementation markedly increases the levels of brain-derived neurotrophic factor (BDNF) of treated 3xTg-AD mice. A single-case pilot study in an AD patient showed that the augmentation of oral zinc (15 mg/day) with vitamins A and D in combination (in Recommended Daily Allowance [RDA] concentrations) raised the plasma zinc level. In order to verify this result, a follow-up study was performed in 70 healthy volunteers (Potocnik et al., 2006). Plasma zinc levels increased significantly ($p < 0.02$) from 11.82 (+/-2.60) to 13.32 (+/-3.04) µmol/L only in the group receiving the combination of zinc and vitamins A and D. This novel method of increasing plasma zinc levels by the augmentation of vitamins A and D may have implications for the reduction of burden of disease. A recent study of Brewer (2012) demonstrated that 6 months of zinc therapy resulted in significant benefit relative to placebo controls in two cognitive measuring systems. It has been suggested that zinc may act by lowering copper toxicity or by a direct benefit on neuronal health.

Conclusion

While many lose ends and conflicting results still exist regarding the role of magnesium and zink deficiency in neuropsychiatric disorders the authors are of opinion that the evidence gathered thus far is more than sufficient to warrant further exploration of this interesting concept, especially in an ageing population.

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