

ZINC NUTRITURE AS RELATED TO BRAIN

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Zn's effect on neurotransmission is in part related to its role in a special class of glutaminergic neurons that have Zn containing vesicles in their presynaptic terminals. With a few exceptions, such as certain cerebrocortical systems, these neurons are located in the telencephalon (Frederickson and Moncrieff, 1994). Glutaminergic systems that do not have Zn containing vesicles include the brain stem, thalamus, and cerebellum. Within the telencephalon, fiber systems with Zn containing vesicles form an associational network that reciprocally interconnects isocortical, allocortical and 'limbic' structures. Hippocampal, amygdalar, and perirhinal regions are prominent components of this network. In hippocampus about 8% of Zn in the hippocampus is in vesicles (Frederickson *et al.*, 1982). Vesicle uptake and release of Zn is impulse-dependent (Howell *et al.*, 1984). Uptake by vesicles is facilitated by a Zn-transporter (ZnT-3) membrane protein (Palmiter *et al.*, 1996). Zn released from vesicles modulates the excitability of post-synaptic N-methyl-D-aspartate (NMDA)-specific (Peters *et al.*, 1987) receptors for glutamate in a dose-dependent and reversible manner. Dietary Zn deficiency decreases the number of glutamate activated NMDA mediated calcium channels in post-synaptic terminals (Browning and O'Dell, 1995). In addition reversible chelation of Zn in the hippocampus impairs spatial-working-memory (Frederickson *et al.*, 1990).

Processes that control release of vesicle Zn are disrupted by seizures (Frederickson *et al.*, 1989) or ischemia (Tonder *et al.*, 1990). Subsequent post-synaptic Zn uptake causes post-synaptic neuronal degeneration. Excess Zn released from vesicles also enters the extra-cellular fluid space (Perez-Clausell and Danscher, 1986). *In vitro* studies show that

high concentrations of Zn destabilize amyloid protein precursor and A-beta-1-40 in the extra-cellular fluid, to form amyloid (Bush *et al.*, 1994).

Metal binding proteins, metallothioneins 1, 2, and 3, sequester Zn (Gasull *et al.*, 1994; Hao *et al.*, 1994; Masters *et al.*, 1994). *In vitro* studies have shown that oxidation of MT by glutathione disulfide (GSSG) releases Zn to Zn binding ligands and that reduced glutathione (GSH) and ATP facilitate the process (Jiang *et al.*, 1998a; Jiang *et al.*, 1998b). Certain selenium compounds also oxidize MT and release Zn (Jacob *et al.*, 1999). Relevant to neurotransmission, Zn released from MT is bound by ATP. Zn-ATP reacts with pyridoxal kinase and pyridoxine to form pyridoxal-5-phosphate (PLP) (Churchich *et al.*, 1989) the co-enzyme for synthesis of biogenic amines (Dakshinamurti *et al.*, 1990). Zn-ATP also reacts with flavo-kinase and riboflavin to form FMN the precursor of FAD (Yamada *et al.*, 1990). FAD is the co-enzyme for MAO degradation of biogenic amines (Hsu *et al.*, 1988).

Zn nutriture affects growth and development of brain. The mechanisms include synthesis of nucleic acids and proteins (Duerre *et al.*, 1977; Fosmire *et al.*, 1974; Lieberman and Ove, 1962; Sandstead *et al.*, 1975). Zn deprivation in early gestation causes neural tube defects (Hurley and Swenerton, 1966; Swenerton *et al.*, 1969; Warkany and Petering, 1972). Zn deprivation during late gestation (McKenzie *et al.*, 1975) and postnatal development impair brain growth (Buell *et al.*, 1977) and cause histologic teratology (Dvergsten, 1984). Abnormalities include a 60% decrease in the number of granule cells relative to Purkinje cells and an associated decrease in the dendritic growth of Purkinje, basket and stellate cells. Height of the dendrite arbor is reduced and there were fewer branches. The number of asymmetric synapses between parallel fibers (axons of granule cells) and dendrites of the Purkinje, basket and stellate cells are decreased about 40%.

Severely Zn deficient rats display poor performance of a simple water maze (Caldwell *et al.*, 1970; Hesse *et al.*, 1979) and impairs mossy fiber evoked potentials (Hesse, 1979). Moderate acute Zn deprivation impairs complex behaviors of rats (Massaro *et al.*, 1982). In rhesus monkeys "moderate" Zn deprivation impairs prepubertal and adolescent behaviors such as activity, attention, and memory tasks before growth is impaired and other overt signs of deficiency are evident (Golub *et al.*, 1995).

Zn deprivation during brain development adversely affects subsequent adult behaviors (Golub *et al.*, 1995; Halas and Eberhardt, 1987). Abnormalities in rat offspring include poor maze learning, poor shock avoidance, increased aggression after shock, and poor working memory of a radial maze task. In rhesus monkeys mild Zn deprivation throughout gestation and the first year of life caused lethargy, apathy, and hypo-activity (Golub *et al.*, 1995).

Severe Zn deprivation in humans impairs taste and smell, and causes ataxia and abnormal mentation including depression, hallucinations and paranoia (Henkin *et al.*, 1975). Patients with acrodermatitis enteropathica may behave abnormally (Moynahan, 1976) and patients given insufficient Zn in long term intravenous or oral feeds may show abnormal behaviors (Kay *et al.*, 1976; Pekarek *et al.*, 1979). Severe maternal Zn deficiency during gestation from acrodermatitis enteropathica has been associated with brain malformations (Hambidge *et al.*, 1975). Findings from Turkey suggest low maternal Zn status during gestation may be associated with fetal anencephaly (Çavdar *et al.*, 1983; Çavdar *et al.*, 1988).

Limited data suggest postnatal performance of infants can be related to maternal diets during gestation. In Egypt infants of women whose diets contained more animal protein and Zn had higher scores on the Brazelton Neonatal Development Assessment

Scales soon after birth (Kirksey *et al.*, 1991). Six months later their motor development, by the Bayley Scales of Infant Development, was inversely related to maternal intake of diets that were low in animal protein and Zn (Kirksey *et al.*, 1994).

Limited observations in infants suggest Zn nutriture affects performance. For example, subjects from a group of 52 very-low-birth-weight (<1,500 g) infants who were given 11 mg Zn/L in formula displayed superior growth and motor development (Griffiths Developmental Assessment Test) compared to subjects given 6.7 mg (Friel *et al.*, 1993). In another study 205 low birth weight low-income Brazilian infants given placebo, 1 mg, or 5 mg Zn 6 days per week for the first 8 weeks of life had similar scores on Bayley Scales of Infant Development at 6 and 12 months of age (Ashworth *et al.*, 1998). However at 12-months of age the five behavior ratings were significantly higher in the infants who had been supplemented with 5 mg Zn. In a third study, a double-blind randomized controlled trial (RCT) of 85 Guatemalan infants, aged 6–9 months, found similar effects on motor development after placebo or 10 mg Zn daily for 7 months (Bentley *et al.*, 1997). However after 7 months the Zn-group sat up, played more, and was less likely to cry or whine.

Few studies of children have been reported. In about 150 children from the Eastern Shore of Maryland, the concentration of Zn in hair was directly related to reading performance and frontal lobe EEG coherence (Thatcher *et al.*, 1984). Three double blind RCTs found that Zn repletion, given with other potentially limiting nutrients, improved neuropsychological function (see details below). In contrast two double blind RCTs found no improvement in performance of tasks that focused on attention (Cavan *et al.*, 1993; Gibson *et al.*, 1989). One suspects that limitations in the methods for assessment contributed to these findings.

The first RCT, above, studied 740 low-income urban Chinese children, aged 6–9 (Sandstead *et al.*, 1998). The ZnM group had fewer missed targets and more hits than either Zn or M groups on the Continuous Vigilance task (a measure of sustained attention). The ZnM group needed fewer trials and less time to learn concepts on the Oddity task (a measure of reasoning). The ZnM group had more time on targets following the most difficult trajectories on the Tracking task (a measure of eye-hand coordination). Both the Zn and ZnM groups had more taps on multiple-key sequences than did the M groups on the Tapping task (a measure of gross motor speed, fatigue and anticipation). The ZnM group had more taps than M, but not Zn, on single key trials that measured fine motor speed and fatigue. The second RCT studied 540 low-income semi-rural Chinese children aged 6–9 years (Penland, 1999). The findings were generally similar to those in the urban children. The third RCT measured neuropsychological performance in 240 low-income Mexican-American children, aged 6–9 years (Penland *et al.*, 1999). The tasks were similar to those administered in China. In contrast to the Chinese subjects only one task was significantly affected. Greatest improvement (decrease in number of errors) in the reasoning task (solving oddity problems) occurred after treatment with ZnM. The ANOVA for interaction, change x treatment, was significant ($p = 0.041$). Changes by treatment were P, -10%; M, -11%; ZnM, -27%; FeM, -10%. Change after ZnM was greater than all others ($p < 0.03$). Likely causes for the differences from China include less severe Zn deficiency, and the smaller number of subjects.

Few studies examined effects of Zn nutriture on neuropsychological functions of adults. An example is a double-blind randomized depletion-repletion study of 11 men who lived under highly controlled conditions (Penland, 1991). In random order they were fed 1, 2, 3, or 4 mg Zn daily for intervals of 35 days. Then they were repleted with 10 mg

Zn daily for 35 days. During depletion performance of 9 of 15 neuropsychological tasks deteriorated. Effects of the four low Zn diets were similar.

Relevant to the elderly Burnet (Burnet, 1981) suggested low Zn nutriture can contribute to the occurrence of dementia. He based his thesis on Zn's essentiality for synthesis and repair of DNA. Supportive of this thesis Tully *et al.* (Tully *et al.*, 1995) found in 12 elderly women that their plasma Zn concentrations one year before death were significantly inversely related to the number of senile and other plaques present in their brains at autopsy.

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