S-18-1

Zinc: Brain Maturation and Function

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The report in 1920 of 40 mg of zinc (Zn) /Kg of brain tissue [2, 29] preceded description of the essentiality of Zn for animals [39] by 14 years. Histologic evidence of Zn in the mossy fiber system of the hippocampus [6] was reported in 1955 [23] as was naturally occurring Zn deficiency in swine [41]. Soon after, malformations of the brain were found in chicks from Zn deprived hens [1]. These findings were explained by the essentiality of Zn for synthesis of nucleic acids and proteins [20, 21, 42]. About the same time, findings in Egyptian and Iranian adolescents revealed Zn deficiency as the cause of growth stunting and delayed sexual maturation [15, 28, 34]. Later, severe Zn deprivation in rats was shown to impair thymidine incorporation into neural crest of embryos [38] and to cause teratology of the brain [18]. A related finding was suppression of thymidine incorporation into brain DNA of 10 day old suckling rats [33]. Estimates of Zn requirements and reported dietary intakes suggested that some pregnant women and infants were Zn deficient [30]. A subsequent study on Swedish women found Zn deficiency in pregnancy [19].

The above prompted us to study of Zn deficiency in rats during latter gestation, suckling and after weaning. Severe maternal Zn deprivation (< 1 mg Zn / Kg diet) from the 14th through the 20th day of gestation caused stunting, and lower levels of DNA ($p < 0.05$) in brains of fetuses [24]. Nutritionally rehabilitated males displayed impaired ($p < 0.01$) avoidance of shock while litter mate females performed as well as the controls [14]. Rehabilitated females showed increased aggression in response to shock ($p < 0.001$) [10, 13]. The executive rat paradigm caused many gastric ulcers in the previously Zn deprived offspring [8].

Severe Zn deprivation from birth to weaning impaired acquisition of an elevated Tolman Honzig maze by adult offspring ($p < 0.01$) [22]. Food motivation of the Zn deprived group was increased compared to *ad libitum* controls, but was less than that of food restricted controls [7]. Reference memory of shock applied on days 18, 19, 20, or 21 of Zn deprivation was impaired ($p < 0.01$) on the 40th postnatal day [11]. Working memory of a 17 arm radial maze was also impaired ($p < 0.001$) in adult offspring [9]. Histologic examination of the cerebellum on the 21st postnatal day found delayed maturation and little migration of external granular cell neurons [3, 4], grossly abnormal arborization of Purkinje Cell dendrites, and decreased numbers and abnormally shaped boutons [5].

Experiments were also done in mildly Zn deprived rats. The dams were fed 10 mg Zn/Kg diet throughout pregnancy and lactation. Pair-fed or *ad libitum*-fed control dams were fed 25 mg Zn/Kg diet. After weaning pups were fed a Zn adequate diet to 300 days of age. Working memory was measured using the 17 arm radial maze food reward paradigm [12]. Memory was impaired in the Zn deprived group ($p < 0.001$); the two control groups were

similar. Histologic examination with toluidin blue of hippocampus of 300 day litter mates found dark staining granular cell neurons in the Zn deprived group [17, 47].

Zinc deprivation of weanling rats increased brain catecholamines [43], copper and manganese [45]. Zinc levels were not affected except in the olfactory bulb where they decreased. Zinc deprivation caused anorexia and cyclic feeding with food intake related to the level of plasma zinc but not to plasma amino acids, glucose, and fatty acids [44]. Brain tryptophane [46] and serotonin were increased [36]; tyrosine was marginally increased [46].

Zn deficiency in rhesus monkeys throughout most of the latter third of gestation impaired exploration and play during weaning of the infants ($p < 0.01$) [35]. Testing with complex learning sets found inferior performance at 300 and 700 days, but not at 1000 days [37].

In humans Zn deficiency causes congenital malformations, small baby size, maternal hypertension, and infant and maternal complications [31]. A recent study found a $> 8 \times$ increased risk of fetal growth retardation among poor women with plasma Zn in the lowest quartile [26].

Little research has been reported on the effects of Zn deficiency on human brain. Evidence was reported in 1977 [16]. Zn deficiency was induced by large doses of histidine. Massive zincuria occurred and subjects showed ataxia, dysgeusia, dysosmia, nyctalopia, and disturbed mentation. Zn repletion restored function.

We induced mild Zn deficiency in 9 men [40]. Accuracy of backward recall of digits was inversely related to plasma Zn ($n=100$, $r=-0.37$, $p<0.001$); Zn retention was inversely related to accuracy ($n=94$, $r=-0.50$, $p<0.001$) and speed ($n=94$, $r=-0.38$, $p<0.001$) of immediate recall of verbal and visual information. The latter findings disappeared when Zn nutriture was repleted.

Recently impaired neuropsychological function was reported in 14 men who were Zn depleted [27]. For 7 months the men were fed diets in random order that provided 1, 2, 3, 4, or 10 (control) mg Zn/day for intervals of 35 days. Significant ($p < 0.05$) decreases in function occurred in 2 sensory-motor tasks (pursuit and trials), 2 attention tasks (orienting and misdirection), 3 perceptual tasks (search, time estimate and Sternberg), 2 memory tasks (shape and cube recognition), and 1 spatial task (maze). Abnormalities were evident at all levels of Zn deprivation. The men also had impaired ethanol metabolism [25] but no decrease in plasma or WBC Zn (Milne, personal communication, 1991).

We [32] measured serum ferritin and plasma Zn in non-anemic premenopausal women, ages 19-40 y, and found lower mean plasma Zn ($p<0.003$) in women with serum ferritin < 20 mg/L ($n= 32$) compared to women with serum ferritin > 20 mg/L ($n= 11$).

The sideropenic women were enrolled in an 8 week double blind randomized controlled study of effects of Fe (30 mg) and/or Zn (30 mg), and/or a vitamin-mineral (VM) treatment on working memory (Wechsler Memory Scale No.1 & 2 (WMS). Normal ferritin women were given VM. Tests of function were done on the 8th day of the menstrual cycle.

The number of subjects in each treatment and % change in the raw WMS scores are shown in Figure 1. The overall power was 90%, assuming a 5% probability of a type I error and a 10% difference in test scores. The power of the findings in the sideropenic women given VM was 80%.

Fe repletion of sideropenic subjects improved immediate recall of verbal material 21.2 % after Fe ($p<0.009$) and 18.7% after Fe & Zn ($p<0.098$); in normal

ferritin women VM was associated with a 26% increase ($p < 0.001$). Sideropenic women given Zn, or only VM had no significant increase in score. However overall power was only 50%, therefore negative findings must be interpreted with caution.

Zn and Fe improved short term memory of visual designs 17.9 ($p < 0.004$) and 20% ($p < 0.03$) respectively (Figure 2). The overall power was 68%. The power for the sideropenic VM group was 71%. Only Zn improved immediate recall of word pairs. The change was 11.4 % ($p < 0.07$). The power for the Zn group was 96%, but for the sideropenic VM group was 34%.

These findings, and those in men experimentally deprived of Zn indicate mild Zn deprivation can impair cognition of humans. Future research will show the significance of these findings for daily living.

ACKNOWLEDGEMENT

I wish to express my gratitude to colleagues that have worked with me on the research noted above. Their contributions to the work have been invaluable.

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