Abstract


Dietary Zinc Regulates Apoptosis through the Phosphorylated Eukaryotic Initiation Factor 2α/Activating Transcription Factor-4/C/EBP-Homologous Protein Pathway during Pharmacologically Induced Endoplasmic Reticulum Stress in Livers of Mice.

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BACKGROUND: Several in vitro studies have shown that zinc deficiency could induce endoplasmic reticulum (ER) stress, resulting in activation of the unfolded protein response.

OBJECTIVE: We aimed to determine whether consumption of a zinc-deficient diet (ZnD) triggers ER stress and to understand the impact of dietary zinc intake on ER stress-induced apoptosis using a mouse model.

METHODS: Young adult (8-16 wk of age) male mice of strain C57BL/6 were fed either a ZnD (<1 mg/kg diet), or a zinc-adequate diet (ZnA; 30 mg/kg diet). After 2 wk, liver, pancreas, and serum samples were collected and analyzed for indexes of ER stress. In another experiment, mice were fed either a ZnD, a ZnA, or a zinc-supplementation diet (ZnS; 180 mg/kg diet). After 2 wk, vehicle or tunicamycin (TM; 2 mg/kg body weight) was administered to mice to model ER stress. Liver and serum were analyzed for indexes of ER stress to evaluate the effects of zinc status.

RESULTS: Mice fed a ZnD did not activate the apoptotic and ER stress markers in the liver or pancreas. During the TM challenge, mice fed a ZnD showed greater C/EBP-homologous protein expression in the liver (3.8-fold, P < 0.01) than did ZnA-fed mice. TM-treated mice fed a ZnD also had greater terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end labeling-positive cells in the liver (2.2-fold, P < 0.05), greater hepatic triglyceride accumulation (1.5-fold, P < 0.05), greater serum alanine aminotransferase activity (1.6-fold, P < 0.05), and greater protein-tyrosine phosphatase 1B activity (1.5-fold, P < 0.05), respectively, than did those fed a ZnA. No significant differences were observed in these parameters between mice fed ZnAs and ZnSs.

CONCLUSIONS: Consumption of a ZnD per se is not a critical factor for induction of ER stress in mice; however, once ER stress is triggered, adequate dietary zinc intake is required for suppressing apoptotic cell death and further insults in the liver of mice.

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