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Magnesium regulates reticular NADPH production in the hepatocyte; Possible implications of magnesium in diabetes and obesity onset

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The current western diet is approximately 35% deficient in magnesium (Mg^{2+}). Magnesium deficiency has been correlated with the onset and progression of several pathological conditions including diabetes, and obesity. As opposed to other clinical electrolytes, Mg^{2+} is not given the same attention clinically due to the poor understanding of its homeostasis. The hormonal regulation of magnesium has not been fully elucidated, and we continue to interpret the serum concentrations relative to urinary Mg^{2+} excretion. Also, our understanding of the extra- and intra-cellular role of Mg^{2+} is further complicated by the fact that the principal reservoir of Mg^{2+} (i.e., the bone) are not readily exchangeable with circulating Mg^{2+} in the extracellular fluid space. Thus, in states of a negative Mg^{2+} balance, initial losses come from the extracellular space since equilibrium with bone stores does not begin for several weeks. The long term goal of this research is to elucidate the implications of magnesium deficiency for liver and whole body metabolism. Our laboratory has previously reported that Mg^{2+} deficiency increases G6P transport into the liver ER, and its hydrolysis by G6Pase. The study reported here evaluates the role of Mg^{2+} deficiency on G6P conversion by Glucose-6-Phosphate Dehydrogenase (G6PD), the other intrareticular metabolic pathway for G6P, and its connection with 11β-Hydroxysteroid Dehydrogenase 1 (11β-HSD1), the NADPH-dependent enzyme responsible for the conversion of cortisone to cortisol. Both enzymes have been implicated in diabetes and obesity onset and progression. The results reported here validate our working hypothesis that a deficiency in hepatic Mg^{2+} content enhances the activities of both G6PD and 11β-HSD1within the lumen of the hepatic endoplasmic reticulum.

Methods: Minimal deviation hepatocellular carcinoma cell line (HepG2-C34) were grown in media containing 0.2 mM, 0.4 mM (deficient) and 0.8 mM (physiological) [Mg^{2+}] acutely (i.e. 5 days), and analyzed for NADPH production by fluorescence detection (350 nm excitation; 460 nm emission). NADPH production was induced by addition of varying concentrations of glucose 6-phosphate to digitonin-permeabilized cells. G6PD, G6Pase, and 11β-HSD1 expression levels were analyzed by western blot analysis for up- or down-regulation following Mg^{2+} deficiency onset. Production of cortisol from cortisone as a measure of the activity of 11β-HSD1 was analyzed by reversed phase HPLC.

Results: NADPH production increased by ~60% under conditions of Mg^{2+} deficiency compared to cells presenting physiological levels of Mg^{2+}, and resulted in a marked increase in cortisol production through 11β-HSD1 activity.

Conclusion: Deficiency in Mg^{2+} appears to upregulate the utilization of G6P by G6PD for energetic purposes, with increased synthesis of NADPH. In turn, the increased level of intrareticular NADPH will favor the conversion of cortisone to cortisol. Increased cortisol production can explain – at least in part- the insulin resistance observed in several diabetic and/or obese conditions. Validation of these results in human patients represents the next step in our studies.

Biography

Chesinta B. Voma is a doctoral student in Bioanalytical and Clinical Chemistry at Cleveland State University. Her thesis research is being conducted at Case Western Reserve University, Cleveland, OH. In addition to her academic pursuit, she works as an ASCP certified medical technologist in a community based hospital laboratory and at an emergency department laboratory of a privately-owned hospital. She is a member of American Association for Clinical Chemistry, The Obesity Society and the Endocrine Society. Her research interest is focused on discovery of new biomarkers that will facilitate early identification and diagnosis of metabolic diseases.

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