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Mg^{2+} deficiency results in increased intra-hepatic cortisol production through the H6PD/11-β-HSD1 machinery: Role of NF-kB and inflammatory cytokines

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Tissue and serum Mg^{2+} deficiency have been observed in several endocrine pathologies including diabetes and metabolic syndrome, but it is still undefined to which extent an altered Mg^{2+} homeostasis contributes to the onset of these pathologies and/or their complications. In the present study, we report that Mg^{2+} deficient hepatocyte exhibit an increased entry of G6P into the endoplasmic reticulum, where the substrate is oxidized by the H6PD to generate NADPH. As H6PD operates in conjunction with 11β-HSD1, the increased level of NADPH is utilized by the latter enzyme to convert inactive cortisone to active cortisol. Administration of cortisone to Mg^{2+} deficient hepatocytes results in a marked production of cortisol, which in turn enhances gluconeogenesis and alters intrahepatic fatty acid synthesis, thus increasing intrahepatic triglyceride levels. Protein and mRNA expression of H6PD and 11β-HSD1 are both increased 3-4 fold in Mg^{2+} deficient cells. Mg^{2+} deficient hepatocytes also exhibit decreased insulin responsiveness, which is further compromised by cortisol production. Returning cellular Mg^{2+} content to its physiological levels, results in a dramatic decrease in cortisol production, and in the progressive renormalization of expression and activity of H6P, 11β-HSD1, and cortisol-responsive genes. Investigation into the underlying mechanism of action suggest that under Mg^{2+} deficient conditions 11β-HSD1 expression and activity increase as a consequence of increased nuclear translocation of NF-kB and increased expression of inflammatory cytokines (namely IL-1β and/or TNFα). Taken together, our results suggest that by increasing H6PD and 11β-HSD1 activity and expression, Mg^{2+} deficiency sets the conditions for an increased intrahepatic production of cortisol and decreased insulin responsiveness. This altered hormonal balance can play a major role in the onset and progression of the metabolic syndrome and its associated complications.

Biography

Andrea Romani, MD, PhD, obtained his Medical Degree from the University of Siena, Italy and his PhD from the University of Turin, Italy. Upon completing his Postdoctoral studies under Dr. Scarpa, he joined the faculty in the Department of Physiology and Biophysics, Case Western Reserve University, where he is currently Associate Professor. He has published almost 90 peer review articles in high profile journals together with numerous invited reviews and book chapters. He is currently serving as an Editorial Board Member for *Archives of Biochemistry and Biophysics, Magnesium Research, World Journal of Gastro-Intestinal Physio-Pathology* among others.

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