

Endocrinology

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Increased cortisol production through the H6PD/11- β -HSD1 machinery in Mg²⁺ deficient liver cells: Role of NF- κ B and inflammatory cytokines

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Tissue and serum Mg²⁺ deficiency have been observed in several endocrine pathologies including diabetes and metabolic syndrome, but it is still undefined to which extent an altered Mg²⁺ homeostasis contributes to the onset of these pathologies and/or their complications. In the present study, we report that Mg²⁺ 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 11 β -HSD1, the increased level of NADPH is utilized by the latter enzyme to convert inactive cortisone to active cortisol. Administration of cortisone to Mg²⁺ 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 11 β -HSD1 are both increased 3-4 fold in Mg²⁺ deficient cells. Mg²⁺ deficient hepatocytes also exhibit decreased insulin responsiveness, which is further compromised by cortisol production. Returning cellular Mg²⁺ content to its physiological levels, results in a dramatic decrease in cortisol production, and in the progressive renormalization of expression and activity of H6PD, 11 β -HSD1, and cortisol-responsive genes. Investigation into the underlying mechanism of action suggest that under Mg²⁺ deficient conditions 11 β -HSD1 expression and activity increase as a consequence of increased nuclear translocation of NF- κ B and increased expression of inflammatory cytokines (namely IL-1 β and/or TNF β). Taken together, our results suggest that by increasing H6PD and 11 β -HSD1 activity and expression, Mg²⁺ 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. After completing his Post-doctoral studies, he joined the faculty in the Department of Physiology and Biophysics, Case Western Reserve University, where currently he is an 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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