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## Increased cortisol production through the H6PD/11-β-HSD1 machinery in Mg<sup>2+</sup>-deficient liver cells

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T issue 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. The H6PD is regarded as an ancillary enzyme for the NADPH-dependent 11 $\beta$ -HSD1, which converts 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 11 $\beta$ -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, 11 $\beta$ -HSD1 and cortisol-responsive genes. Taken together, our results suggest that by increasing H6PD and 11 $\beta$ -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 M P 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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