Obesity-2013

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference and Exhibition on
Obesity & Weight Management

December 02-04, 2013 Hampton Inn Tropicana, Las Vegas, USA

Decrease in hepatic Mg^{2+} content promotes cortisol production in liver cells: Implications for the metabolic syndrome onset

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Abstract

Metabolic Syndrome, also known as Syndrome X, is a pathological condition affecting approximately 25% of the USA population. The condition is characterized by obesity, insulin resistance, and various degrees of hypertension.Metabolic syndromeis considered as the single most common condition predisposing to the development of various chronic diseases including diabetes and hypertension. Hypomagnesaemia has been consistently observed in association with metabolic syndrome, but it is unclear whether reduced Mg^{2+} levels arethe consequence or a possible cause for the development of the metabolic syndrome and/or its associated pathologies.

Recent research in our laboratory indicates that low Mg^{2+} level in the circulation and within the hepatocytes promotes dysmetabolic conditions typical of the metabolic syndrome. Rats exposed for 2 weeks to a 40% Mg^{2+} deficient diet present a 2-3 fold increase in intrahepatic triglyceride content, SREBP1c activation, PPAR□upregulation, decreased glucose accumulation, and attenuated insulin signaling. Reduced intrahepatic total and free Mg^{2+} content stimulates glucose 6-phosphate (G6Pi) transport into the endoplasmic reticulum (ER) and results in enhanced G6Pi hydrolysis by the glucose 6 phosphatase (G6Pase). More importantly, the increased G6Pi transport results in an enhanced conversion of G6Pi to 6-phosphogluconolactone by the glucose 6 phosphate dehydrogenase (G6PD), with generation of higher than normal intraluminal NADPH level. This pyridine nucleotide pool is utilized in several intraluminal processes including the conversion of cortisone to cortisol by the 11-□-hydroxysteroid dehydrogenase type 1 (11-□-OHSD1). In fact, we observed a significant, inverse correlation between hepatic Mg^{2+} content and cortisol production.

Taken together, our results provide compelling evidence that reduced extracellular Mg^{2+} level precedes and promotes metabolic syndrome onset in that: 1) liver metabolism undergoes a switch from glucose-based to fatty acid-based metabolism, with increased deposition of intrahepatic triglycerides; 2) increased cortisol production, and 3) reduced insulin responsiveness. Work is currently in progress to determine whether restoration of normal extracellular or dietary Mg^{2+} content renormalizes hepatic Mg^{2+} content, and returns the mentioned metabolic processes to physiological levels, and whether our observation can be exported to other liver-based diseases such as alcoholic and non-alcoholic liver steatosis and steatohepatitis. [Supported by NIAAA-11593 and HL 090969]

Biography

Andrea Romani has completed his Ph.D at the age of 30 years from the University of Turin, Italy and postdoctoral studies from Case Western Reserve University School of Medicine. He is Associate Professor in the Department of Physiology and Biophysics at Case Western Reserve University. He has published more than 80 papers and review articles in reputed journals and is serving as an editorial board member of repute for journal such as Archives of Biochemistry and Biophysics, Magnesium Research, World Journal of Gastro-Intestinal Physio-Pathology, among others.