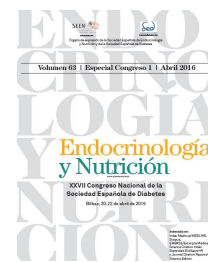




Endocrinología y Nutrición



O-011. - THE DIABETES-LINKED FACTOR HMG20A TARGETS ISLET GENES INVOLVED IN INSULIN SECRETION

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Resumen

Introduction and objectives: Recent genome-wide association studies (GWAS) have identified *HMG20A* as a susceptibility locus for type 2 diabetes mellitus (T2DM). This gene encodes a factor that binds chromatin and exerts global genomic changes. Thus the role of *HMG20A* in the development and establishment of T2DM is far from evident. To assign a function to *HMG20A* in islet physiology, we aimed herein to: 1) Assess the expression levels of *HMG20A* in islets and whether acute or chronic exposure to glucose alters these levels and 2) determine the impact of *HMG20A* on glucose-stimulated insulin secretion (GSIS).

Material and methods: *HMG20A* transcript levels were assessed by quantitative PCR (QT-PCR) in various tissues under basal or high glucose concentrations. Protein levels were also assessed by immunohistochemistry in islets. To evaluate the effect of *HMG20A* on beta cell function, expression levels of potential targets involved in insulin biosynthesis and secretion such as *NEUROD*, *SNAP25*, *SYTVII*, *PI3K*, *Glucokinase (GK)*, *GLUT-1* and *GLUT-2* were measured following 72 hours of siRNA-mediated repression of *HMG20A* in MIN-6 and INS-1 cells. Data mining for *HMG20A* expression levels in both Type 1 (T1DM) and T2DM patients was performed using the Nextbio database from Illumina (www.nextbio.com).

Results: High levels of *HMG20A* were detected in islets as compared to muscle and adipose tissue, whereas the transcript was more abundant in the liver. *HMG20A* protein was detected in mouse and human beta cells as well as in other islet cell types. Short-term exposure to glucose induced a transient increase in *HMG20A* transcript levels reaching a maximum of 2-fold at 72 hours in human islets with similar results in MIN-6 cells. However, expression of *HMG20A* was decreased in T2DM and T1DM patients as compared to non-diabetic subjects. siRNA-mediated repression of *HMG20A* in MIN-6 as well as in INS-1 cells resulted in decreased expression of *NEUROD*, *INSULIN*, and *GK* whereas *PI3K* and *GLUT2* were increased. In parallel, GSIS was impaired following siRNA-mediated *HMG20A* repression in INS-1 cells.

Conclusions: *HMG20A* modulates GSIS through regulation of metabolism-secretion coupling genes.

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