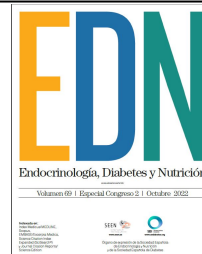




Endocrinología, Diabetes y Nutrición



6 - REGULATION OF INSULIN SIGNALING BY HNRNPK

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Resumen

Insulin resistance defines as an impairment in the biologic response to insulin action in target tissues, primarily the liver, muscle, adipose tissue, and brain. Insulin resistance affects physiology in many ways, causing many pathologic states such as dyslipidemia, visceral adiposity and hyperglycemia among others, and its persistence leads to the development metabolic disease, including diabetes, obesity, cardiovascular disease, or nonalcoholic fatty liver disease (NAFLD). In addition to classical transcriptional factors, posttranscriptional control of gene expression exerted by miRNAs and RNA-binding proteins (RBPs) constitutes a new level of regulation with important implications in metabolic homeostasis. Previous studies from our group showed that miR-7, encoded in the RBP hnRNPK (heterogenous nuclear Ribonucleoprotein K), in the inhibition of key targets of the insulin signaling pathway and others involved in Alzheimer Disease. Given the potential cooperative role of unrelated miRNAs and RBPs families, we aimed to explore whether hnRNPK could also influence insulin signaling in neurons and primary mouse hepatocytes and its implication in metabolism *in vivo*. Our initial bioinformatic analysis showed a number of consensus binding sites for this RBP in the 3'UTR of the human and mouse insulin receptor (INSR). Further experiments demonstrated that silencing hnRNPK both in neuronal cell lines as well as in mouse primary hepatocytes blunted intracellular insulin cascade and levels and subcellular location of INSR in the plasma membrane. Further analysis included the specific *in vivo* silencing of hnRNPK in the liver in mice fed in chow and high fat diet (60 kJ% Fat) that promoted an impairment of systemic glucose metabolism, changes in body weight, adiposity and lipid accumulation in the liver. Overall, these results describe the novel contribution of hnRNPK in regulating metabolism through the insulin signaling pathway.