Endocrinol Diabetes Nutr. 2018;65(Espec Cong 1):22

Endocrinología, Diabetes y Nutrición

O-022 - HMG20A, BRIDGING BRAIN AND ISLET IN INSULIN EXPRESSION AND GLUCOSE HOMEOSTASIS

E. Fuente-Martín[a], J.M. Mellado-Gil[a], N. Cobo-Vuilleumier[a], S.Y. Romero-Zerbo[b], F.J. Bermúdez-Silva[c], J.C. Reyes[a] y B.R. Gauthier[a]

[a]Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Sevilla. [b]IBIMA-Hospital Regional Universitario de Málaga-Universidad de Málaga, Málaga. [c]IBIMA-Hospital Regional Universitario de Málaga. Universidad de Málaga. CIBERDEM, Málaga.

Resumen

Introduction and objectives: Accumulating evidence indicates that systemic glucose homeostasis is regulated, in part, through a central nervous system (CNS)/islet axis. In analogy to islet beta cells, hypothalamic astrocytes have recently come into the limelight as the glucose sensor that facilitates the CNS response to changing metabolic environment. Therefore, astrocytes and beta cells may share a common genetic signature implicated in coupling glucose metabolism to cellular output. We recently demonstrated that the chromatin-remodeling factor HMG20A is essential for metabolism-insulin secretion coupling via the regulation of key pancreatic islet-enriched genes that establish beta cell functional maturity. As HMG20A is also important for CNS development, we sought to determine whether it might be involved in astrocyte glucose sensing function. To this end, herein we evaluate HMG20A expression and function in astrocytes under various metabolic conditions.

Material and methods: HMG20A transcript levels were assessed by quantitative PCR (RT-PCR) in the hypothalamus of mice exposed to a high-fat diet (HFD). Primary hypothalamic astrocytes cultures from 2 days-old C57Bl/6J mice were exposed to 6 or 22 mM glucose as well as 0.5 mM palmitate for 24 or 48 hours. HMG20A expression levels were then evaluated by RT-PCR. To investigate HMG20A function in astrocytes, expression levels of potential targets involved in glucose sensing such as glucose and lactate transporters as well as lactate secretion were examined after 72 hours siRNA-mediated repression of HMG20A.

Results: HMG20A expression was increased in the hypothalamus of glucose intolerant HFD-fed mice correlating with higher transcript levels of glial fibrillary acidic protein (GFAP), indicative of reactive astrocytes. To determine the contribution of either glucose and/or fatty acids in this process, primary astrocytes were cultured with both substrates. High glucose but not palmitate decreased HMG20A transcript levels. A 60% siRNA-mediated repression of HMG20A increased transcript levels of GFAP, vimentin (a marker of reactive astrocytes) and IL-1beta. Expression levels of GLUT1 and MCT4 were also elevated correlating with higher lactate secretion. Likewise, HMG20A-silenced astrocytes were more vulnerable to apoptosis. This particular genetic signature is a hallmark of reactive astrocytes. Remarkably, insulin was also detected in astrocytes and was modulated by HMG20A. RNAseq is currently being conducted to delineate HMG20A targeted pathways involved in astrocyte phenotypic state.

Conclusions: HMG20A is involved in the reactive astrocyte polarization state. Glucose and not free fatty acids is a key metabolite that modulates HMG20A expression and relays the phenotypic switch of astrocytes. Under chronic stress, HMG20A expression may be increased to prevent aberrant reactive astrocyte cell death, as observed in HFD fed mice. We posit that HMG20A mediates astrocyte transition between reactive and non-reactive state to acutely fine tune glucose metabolism to lactate secretion necessary for neuronal regulation of glucose homeostasis.