IJAE
Vol. 118, n. 2 (Supplement): 142, 2013
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

High glucose impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus

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Rabbits with high fat diet (HFD)-induced metabolic syndrome (MetS) developed hypogonadotropic hypogonadism (HH) and showed a reduced gonadotropin-releasing hormone (GnRH) immunopositivity in the hypothalamus (Filippi et al., 2009). This study investigated the relationship between MetS and hypothalamic alterations in HFD-rabbits. Gonadotropins levels decreased as a function of MetS severity, glucose intolerance, hypothalamic gene expression of glucose transporter 4 (GLUT4) and interleukin-6 (IL-6). HFD significantly induced mRNA expression and hypothalamic immunopositivity of GLUT4 and IL-6, as well as a low-grade hypothalamic inflammation (microglial activation with unchanged astroglia morphology), while reduced hypothalamic immunopositivity for KiSS-1 receptor (KiSS-1R), whose mRNA expression negatively correlated with glucose intolerance. Moreover, high glucose exposure down-regulated KiSS-1/KiSS-1R system and GnRH expression in human GnRH-secreting neuroblasts. A subset of HFD rabbits was treated with the farnesoid-X receptor agonist obeticholic acid, able to ameliorate glucose metabolism (Morelli et al., 2012). This treatment significantly increased GnRH mRNA and reduced GLUT4 and IL-6 immunopositivity. Our results suggest that HFD-induced glucose dysregulation negatively affects GnRH neuron function through an inflammatory injury at the hypothalamic level.

References

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Key words

Glucose intolerance; Hypothalamic inflammation; Metabolic syndrome; GLUT4; IL-6; Hypogonadotropic hypogonadism.