Endocrinol Diabetes Nutr. 2021;68(Espec Cong 2):3

Endocrinología, Diabetes y Nutrición

3 - GRK2 REGULATES PUBERTY ONSET VIA REPRESSION OF KISSPEPTIN SIGNALING IN GNRH NEURONS: IMPLICATIONS FOR THE NUTRITIONAL CONTROL OF PUBERTY

C. Perdices-López[1,2,3], M.S. Avendaño[1,2], A. Barroso[1,2], F. Gaytán[2], F. Ruiz-Pino[1,2], S. León[1,2], F. Mayor Jr[4], C. Murga[4], U. Kaiser[5] and M. Tena-Sempere[1,2,3]

[1]Physiology. Maimonides Biomedical Research Institute of Cordoba. [2]Cell Biology. Physiology and Immunology. Department of Cell Biology. Physiology and Immunology. University of Cordoba. [3]Obesity and Nutrition. Networking Center for Physiopathology of Obesity and Nutrition (CIBERobn). [4]Molecular Biology. Molecular Biology Department. Center of Molecular Biology Severo-Ochoa. Autonomous University of Madrid. [5]Endocrinologym Diabetes and Hypertension. Division of Endocrinology. Diabetes and Hypertension. Brigham and Women's Hospital and Harvard Medical School. Boston, MA. USA.

Resumen

Perturbations in the timing of puberty, with potential adverse consequences in later health, are becoming increasingly common, especially in girls. The underlying mechanisms remain unfolded, but nutritional alterations are key contributors. Here, we disclose a pathway involving the G protein-coupled-receptor kinase-2, GRK2, in GnRH neurons, as major modulator of pubertal timing via repression of the actions of the puberty-activating neuropeptide, kisspeptin, whose receptor, Gpr54, is expressed in GnRH cells. In female rats, hypothalamic GRK2 expression increased along postnatal maturation, especially in the preoptic-area, where most GnRH neurons reside, but decreased during the juvenile-to-pubertal transition. Blockade of GRK2 activity enhanced Ca^{+2} responses to kisspeptin in Gpr54-expressing cells in vitro, while central inhibition of GRK2 in vivo augmented LH and FSH responses to kisspeptin and advanced puberty onset. Postnatal undernutrition increased hypothalamic GRK2 expression and delayed puberty onset, the latter being partially reversed by central GRK2 inhibition. Conditional ablation of GRK2 in GnRH neurons in mice similarly enhanced kisspeptin-responses, accelerated puberty onset, and increased LH pulse frequency, while partially prevented the negative impact of subnutrition on pubertal timing and LH pulsatility. All in all, our data conclusively document that GRK2 negatively regulates kisspeptin signaling in GnRH neurons, as regulatory mechanism for tuning pubertal timing, in normal and metabolically-compromised conditions.