

Tumor necrosis factor alpha impairs kisspeptin signaling in human fetal hypothalamic neurons

Erica Sarchielli¹, Roberta Squecco¹, Paolo Comeglio², Eglantina Idrizaj¹, Stefano Ambrosini¹, Giulia Guarnieri¹, Gabriella Vannelli¹, Annamaria Morelli¹

¹ Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy - ² Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

Previous studies in both human and animal models have linked overnutrition-related metabolic dysfunctions to hypothalamic inflammation (1, 2). Moreover, metabolic disorders are often associated with male hypogonadotropic hypogonadism, suggesting that inflammatory pathways may impair central regulatory networks involving gonadotropin releasing hormone (GnRH) neuron activity. However, studies in humans are strongly hampered by the anatomical distribution of these neurons, scattered within the preoptic area of the hypothalamus. This study was aimed at investigating the effects of inflammatory stimuli in human fetal hypothalamic (hfHypo) primary cell cultures. These cells have shown evident GnRH neuron features, as demonstrated by quantitative gene expression profile, immunohistochemistry, flow cytometry and ELISA detection of GnRH peptide in the culture medium. Moreover, hfHypo cells express KISS1R and accordingly respond to kisspeptin, the main central regulator of GnRH neuron function. Exposing hfHypo cells to TNF α (10ng/ml, 5h) determined nuclear translocation of NF κ B, as well as a significant increase of COX2 mRNA expression, thus demonstrating the induction of inflammatory signaling. Prolonged exposure (24 h) to TNF α strongly down-regulated KISS1R mRNA without changing GnRH expression. Moreover, we know that kisspeptin is able to depolarize GnRH neurons through the activation of a canonical transient receptor potential (TRPC)-like cationic channel. Electrophysiological studies demonstrated that kisspeptin (1 μ M) induced a clear TRPC-mediated depolarizing response in hfHypo cells. Pretreating cells with TNF α (10 ng/ml, 24h) significantly inhibited kisspeptin-sensitive TRPC currents. Our results indicate that inflammatory pathways may impair GnRH neuron function by interfering with the ability of these neurons in responding to kisspeptin.

References

- [1] Thaler et al. (2010) Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest.* 122, 153; doi: 10.1172/JCI59660.
- [2] Morelli et al. (2014) Metabolic syndrome induces inflammation and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits. *Mol Cell Endocrinol.* 382,107; doi: 10.1016/j.mce.2013.09.017.

Keywords

Inflammation; metabolic disorders; GnRH.