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

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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 (hfHy-po) 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, hfHy-po cells express KISS1R and accordingly respond to kisspeptin, the main central regulator of GnRH neuron function. Exposing hfHy-po cells to TNFα (10ng/ml, 5h) determined nuclear translocation of NFkB, as well as a significant increase of COX2 mRNA expression, thus demonstrating the induction of inflammatory signaling. Prolonged exposure (24 h) to TNFα 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 µM) induced a clear TRPC-mediated depolarizing response in hfHy-po cells. Pretreating cells with TNFα (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


Keywords
Inflammation; metabolic disorders; GnRH.