P112.-Sex differences in gene expression of X-linked histone demethylase Kdm6a in embryonic hypothalamic neurons

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Kdm6a and Kdm5c are histone demethylases that play an important role as epigenetic regulators of gene transcription by removing the di- and tri-methylation of Lys27 or Lys4 on histone H3 (H3K27me2/me3 - H3K4me2/me3). Both demethylases are implicated in regulation of transcription during neuronal growth and differentiation, being possible to hypothesize that they may contribute to generate sex differences in brain since they are encoded by X-linked genes and escape X-chromosome inactivation. Using the Four Core Genotypes (FCG) mouse model, we first analyzed the expression of Kdm6a and Kdm5c genes by RT-qPCR in primary hypothalamic neuron cultures from E15. Only Kdm6a showed differences between genotypes, presenting higher levels of expression in XX than in XY neurons ($p<0.05$), regardless of the embryo sex. Estradiol 10-10 M did not affect such expression pattern in vitro. When we measured Kdm6a mRNA in the ventromedial hypothalamic region of adults, we found only XX males presented higher levels than the other three genotypes. We next evaluated the effect of Kdm6a/b activity inhibitor GSK-J4 on the sexually dimorphic expression of neurogenin 3 (Ngn3), a gene involved in the neuritogenesis of cultured hypothalamic neurons. Our preliminary results showed that GSK-J4 diminishes Ngn3 expression only in male cultures. Further experiments are required to better understand the role of Kdm6a in generation of sex differences in growth and differentiation of hypothalamic neurons.
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