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IRX3 transcription factor inhibited in hypothalamus generates FTO raises and getting worse obesity by increase inflammatory markers

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Previously described, the transcription factor IRX3 can modulate FTO expression and contribute to obesity. However, little is known about the effect of the consumption of dietary fats (HFD) in hypothalamic IRX3 gene expression and this contribution in peripheral tissues. Therefore, the aim of this work was establish the correlation between IRX3 hypothalamic inhibition, these metabolic repercussions and the modulation of genes involved in inflammation. First, in cell culture experiments we show that IRX3 is expressed in a hypothalamic neuron cell-line (CLU189) but not in a microglia cell line (BV2), and after palmitate stimulation in CLU189 cells we observed alterations in IRX3, AgRP and TLR4 gene expression. In C57Bl6J mice the consumption of HFD resulted in hypothalamic IRX3 reduction accompanied by the increase of FTO expression. In chow, fasting resulted in reduction in IRX3 transcript expression, and followed by increased NPY and AgRP. This effect was blunted after HFD consumption. Lentivirus (LV) was ICV inoculated to inhibit IRX3 in hypothalamus and metabolic outcomes were determined. In mice fed on HFD, the inhibition of hypothalamic IRX3 by LV was accompanied by >1.6-fold in body mass despite caloric intake, spontaneous physical activity and whole body oxygen consumption. Using a thermosensitive camera we did not detected alterations in BAT heat production. UCP1 and β3 adrenergic presented decreased expression, and LV injection increased WAT accumulation in BAT. In WAT IRX3 inhibition in hypothalamus produce modulation in UCP1 and TBX1 gene expression. In conclusion, IRX3 expressed in hypothalamus is regulated by fasting and the consumption of a HFD. Utilizing a PCR Array Mouse Inflammatory Cytokines & Receptors assay, we observed that hypothalamic inhibition of IRX3 increase the expression of genes correlated with inflammation, and it probably should be the cause to these global obesity effects. Hypothalamic-inhibition of IRX3 expression worsens obesity by body mass gain, and presented effect on BAT function and important markers of "browning". Thereby, IRX3 could be an important target to future obesity-treatments.

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