

Novel adipo-miokines irisin and FGF21 modulate hypothalamic control of feeding

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In vertebrates, feeding regulation and energy balance are the results of a complex interplay between hypothalamic neurotransmitters, neuropeptides and peripheral afferents such as adipokines and gut-derived peptides [Kalra et al., 1999]. Irisin, the proteolytic fibronectin type III domain containing 5 (FNDC5)-cleaved product, is a recently identified adipo-myokine that has been indicated as a possible link between physical exercise and energetic homeostasis. The colocalization with neuropeptide Y neurons in the hypothalamic paraventricular nucleus suggested a possible role of irisin in the central regulation of energy balance [Piya et al., 2014; Roca-Rivada et al., 2013]. Fibroblast growth factor 21 (FGF21) is an adipo-miokine that has been involved in the regulation of appetite and energy balance, through both peripheral and central mechanism, albeit the neuronal pathways involved in mediating its effects are not fully elucidated [Kliwer et al., 2010; Sarruf et al., 2010]. In this context, in the present work we studied the effects of intra-hypothalamic irisin and FGF21 administration on orexigenic [agouti-related peptide (AgRP) and neuropeptide Y (NPY)] and anorexigenic [cocaine and amphetamine-regulated transcript (CART) and proopiomelanocortin (POMC)] peptide activity in male Sprague-Dawley rats. Furthermore, we evaluated the effects of each peptide on hypothalamic dopamine (DA), norepinephrine (NE) and serotonin (5-hydroxytryptamine, 5-HT) levels, *in vivo*. Rats were injected into the hypothalamic arcuate nucleus with either 1 μ l vehicle or 1 μ l peptide (5-5000 ng), as previously reported [Sarruf et al., 2010; Moon et al., 2013]. Food intake and hypothalamic neurotransmitter and neuropeptide mRNA levels were evaluated 24 h after treatment. Compared to vehicle, irisin injected rats showed decreased food intake, possibly mediated by stimulated POMC and inhibited DA and NE activity, in the hypothalamus. On the other hand, FGF21 administration increased food intake compared to vehicle, possibly through stimulated DA, NE, NPY and AgRP activity and inhibited 5-HT and POMC activity, in the hypothalamus. Further studies are needed to elucidate the role of irisin and FGF-21 in feeding regulation and their possible involvement in obesity.

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