

Role of lipids on the hypothalamic control of hunger and thermogenesis

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Obesity has reached epidemic proportions in several regions of the world. General changes in life-style, including consumption of fat-rich food, are amongst the most important factors leading to an unprecedented increase in the prevalence of this disease. Weight gain results from an imbalance between caloric intake and energy expenditure. Both of these parameters are under the tight control of specialized neurons of the hypothalamus that respond to peripheral anorexigenic and adipostatic signals carried by leptin and insulin. Here we show, by macroarray analysis, that high-fat feeding (hyperlipidic diet – HL) induces the expression of several pro-inflammatory cytokines and inflammatory responsive proteins in hypothalamus. This phenomenon is accompanied by increased activation of JNK and NF κ B. In addition, HL feeding leads to impaired functional and molecular activation of the insulin-signaling pathway, which is paralleled by increased serine phosphorylation of the insulin receptor and IRS-2. Intracerebroventricular (icv) treatment of HL rats with a specific inhibitor of JNK (SP600125) restores insulin signaling and leads to a reduced caloric intake and weight loss. We conclude that HL feeding induces a local pro-inflammatory status in the hypothalamus, which results in impaired anorexigenic insulin signaling.