Poster

Analysis of the expression of metabolic sensors and inflammation mediators in the brain of animals with genetic obesity exposed to adiponectin activator NP1

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ABSTRACT

Drug treatment strategies that interfere with adipokines secreted by adipose tissue, such as adiponectin and leptin, have been recently developed for treating obesity. Adiponectin is able of reducing both, food intake and body weight through both, its action on the hypothalamus, and concerted actions on glucose and insulin sensitivity, and oxidation of fatty acids in peripheral tissues. Furthermore, in vitro studies have shown that adiponectin attenuates inflammation in endothelial, muscle and macrophage cells. Leptin acts synergistically with adiponectin in the regulation of energy balance, inhibiting food intake, and being its levels regulated in the hypothalamus through the endocannabinoid system and the peptides NPY/AgRP, POMC and orexins. Therefore, the restoration of normal adiponectin levels can be considered a good clinical option for the treatment of obesity. Recently, a new thiazole-derived drug called NP-1 has been described as an adiponectin promoter activator able to promote adiponectin release.

We investigated the effects of NP-1 in the hypothalamus of lean (fa/-) and obese (fa/fa) leptin signaling deficient Zucker rats, after a 15-day exposure to vehicle or NP-1 (5 mg/Kg). Brains were removed and frozen and the hypothalamus was dissected out from a coronal section, following the rodent atlas of Paxinos. Protein extraction was performed from the obtained tissue to analyze it by Western Blot, and RNA was isolated to determine gene expression by RT-qPCR.

Treatment with NP-1 increased circulating TNFα, which led to weight loss through decreased intake. NP-1 reduced the expression of adiponectin and TNF α receptors in the hypothalamus. It also reduced mRNA expression of intake promoters such as NPY, AGRP and hypocretin-1, and a specific obesity-dependent modulation of POMC. Leptin deficiency-induced obesity was associated with specific insulin resistance preventing NP-1-induced sensitization of insulin signaling (Phosphorylation of IRS1 and PI3K) in lean animals. Finally, NP-1 was able to decrease ERK1/ERk2 and NFkB activation, suggesting reduced inflammation of the hypothalamus. In conclusión, NP-1 modulates feeding through increased TNFα and regulation of hypothalamic neuropeptides without increasing inflammation.

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