**Hypothalamic TTF-1 orchestrates the sensitivity of leptin**

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The hypothalamus acts dynamically as the central unit for the regulation of whole body energy homeostasis. Leptin, an adipocyte-derived hormone, is an afferent input to the hypothalamic neuronal circuit that controls energy intake and expenditure. In this study, we interrogated that thyroid transcription factor-1 (TTF-1), a homeodomain-containing transcription factor, mediates the impacts of leptin and is coupled to the pathogenesis of obesity by regulating the responsiveness of the hypothalamic circuit activity in response to circulating leptin. The selective deletion of *TTF-1* gene expression in the hypothalamic neurons that govern the appetite regulation resulted in enhanced sensitivity to leptin: leptin’s anorexigenic effect and the phosphorylation of signal transducer and activator of transcription 3 (STAT3), a downstream molecule of the leptin signaling pathway, were elevated by conditional deletion of TTF-1 in the cells expressing the leptin receptor (ObRb) and proopiomelanocortin (POMC). In line with these findings, the selective deletion of the *TTF-1* gene in ObRb-positive cells gives rise to a protection against diet-induced obesity by ameliorating the leptin resistance. Collectively, these observations suggest that the hypothalamic TTF-1 participates in the development of the obesity phenotype as a molecular component involved in the regulation of cellular leptin signaling and activity.