

**TNF-alpha Converting Enzyme heterozygous mice are protected from obesity-induced insulin resistance and diabetes**

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## Abstract

**Objective:** TNF- $\alpha$  is known to affect insulin sensitivity, glucose and lipid metabolism through alternative and redundant mechanisms at both translational and post-translational levels. TNF- $\alpha$  exerts its paracrine effects once the membrane-anchored form is shed and released from the cell membrane. TNF- $\alpha$  cleavage is regulated by TNF- $\alpha$  Converting Enzyme (TACE), which regulates the function of several transmembrane proteins, such as Interleukin-6 Receptor (IL-6R) and EGF Receptor ligands. The role of TACE in high fat diet induced obesity and its metabolic complications is unknown.

**Research Design and Methods:** To gain insights into the role of TACE in metabolic disorders we used *Tace*<sup>+/-</sup> mice fed with a standard or high fat diet (HFD) for 16 weeks.

**Results:** We observed that *Tace*<sup>+/-</sup> mice are relatively protected from obesity and insulin resistance compared with WT littermates. When fed a HFD, WT mice exhibited visceral obesity, increased FFA and Monocyte Chemoattractant Protein-1 (MCP1) levels, hypoadiponectinemia, glucose intolerance and insulin resistance compared with *Tace*<sup>+/-</sup> mice. Interestingly, *Tace*<sup>+/-</sup> mice exhibited increased UCP-1 and GLUT4 expression in white adipose tissue.

**Conclusions:** our results suggest that modulation of TACE activity is a new pathway to be investigated for development of agents acting against obesity and its metabolic complications.





















