

Abstract Timper et al.

Enhanced CNS IL-6 Trans-Signaling in Obese Mice Sensitizes for IL-6-Dependent Improvement of Energy and Glucose Homeostasis

Introduction: Interleukin (IL)-6 engages similar signaling mechanisms as leptin. Here we demonstrate that central application of IL-6 in mice suppresses feeding and improves glucose tolerance. Furthermore, we found that central IL-6 trans-signaling is enhanced in obese mice to improve anorexigenic and glucoregulatory effects of IL-6.

Methods/Design: Glucose tolerance and insulin sensitivity as well as food intake and pSTAT3 expression were investigated upon central application of IL-6 or Hyper-IL-6, a fusion protein of IL-6 and its soluble receptor, in high-fat diet-fed and chow-fed control mice as well as in mice lacking the IL-6 receptor (IL-6R) in the whole body or in distinct areas of the hypothalamus (Nkx2.1-Cre;IL-6R α -flox mice) or the forebrain (CamKII α -Cre;IL-6R-flox mice). IL-6 trans-signaling in the central nervous system (CNS) was inhibited by intracerebroventricular administration of soluble gp130 (sgp130Fc), an inhibitor of soluble IL-6R α (sIL-6R) complexed with IL-6. Furthermore, the concentration of endogenous sIL-6R was assessed in cerebrospinal fluid (CSF) and plasma of obese and lean mice. Finally gp130 was deleted in the paraventricular nucleus of the hypothalamus (PVH) upon adeno-associated virus (AAV)-injection into the PVH.

Results: In contrast to leptin, the action of which is attenuated upon obesity development, the ability of IL-6 to suppress feeding is enhanced in obese compared to lean mice. Surprisingly, IL-6 suppresses feeding in the absence of classical IL-6R-dependent signaling in neurons of mice lacking the IL-6R either specifically in hypothalamic or in all forebrain neurons. Accordingly, obese mice exhibit increased concentrations of the soluble IL-6 receptor in the cerebrospinal fluid and blocking central IL-6-trans-signaling abrogates the ability of IL-6 to suppress feeding. Furthermore, gp130 expression is enhanced in the PVH of obese mice and deletion of gp130 in the PVH attenuates the beneficial central IL-6 effects on metabolism.

Conclusion: Collectively, these experiments indicate that IL-6-trans-signaling is enhanced in the CNS of obese mice, allowing IL-6 to exert its beneficial metabolic effects even under conditions of leptin resistance.