The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men

Jean L. Chan,[1] Kathleen Heist,[1] Alex M. DePaoli,[2] Johannes D. Veldhuis,[3] and Christos S. Mantzoros[1]

[1]Division of Endocrinology and Metabolism, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[2]Amgen Inc., Thousand Oaks, California, USA
[3]Department of Endocrinology, Mayo Clinic, Rochester, Minnesota, USA

To elucidate the role of leptin in regulating neuroendocrine and metabolic function during an acute fast, six to eight healthy, lean men were studied under four separate conditions: a baseline fed state and three 72-hour fasting studies with administration of either placebo, low-dose recombinant-methionyl human leptin (r-metHuLeptin), or replacement-dose r-metHuLeptin designed to maintain serum leptin at levels similar to those in the fed state. Replacement-dose r-metHuLeptin administered during fasting prevents the starvation-induced changes in the hypothalamic-pituitary-gonadal axis and, in part, the hypothalamic-pituitary-thyroid axis and IGF-1 binding capacity in serum. Thus, in normal men, the fall in leptin with fasting may be both necessary and sufficient for the physiologic adaptations of these axes, which require leptin levels above a certain threshold for activation. In contrast to findings in mice, fasting-induced changes in the hypothalamic-pituitary-adrenal, renin-aldosterone, and growth hormone–IGF-1 axes as well as fuel utilization may be independent of leptin in humans. The role of leptin in normalizing several starvation-induced neuroendocrine changes may have important implications for the pathophysiology and treatment of eating disorders and obesity.

J. Clin. Invest. **111**:1409–1421 (2003). doi:10.1172/JCI200317490.

Introduction

Leptin is an adipocyte-derived hormone whose absence in mice (1) and humans (2–4) causes abnormal energy homeostasis and profound obesity that is ameliorated by leptin treatment (5, 6). Leptin is secreted into the circulation in a highly organized and pulsatile fashion (7). By activating specific leptin receptors in the hypothalamus, leptin alters the expression of several hypothalamic neuropeptides and thereby regulates energy intake and expenditure (8–10). Although leptin was originally thought to function primarily as an antiobesity hormone in leptin-deficient states, subsequent research has suggested an additional and significant role for leptin in signaling changes in energy balance (especially nutritional deprivation) and in regulating the neuroendocrine and metabolic responses to starvation in rodents (8–10).

Short-term fasting results in a rapid and marked decline in leptin levels out of proportion to the loss of fat mass (11, 12), and it has been proposed that this most likely serves as an adaptive mechanism to promote survival and limit procreation during starvation (8). In mice, the exogenous administration of leptin in physiologic replacement doses prevents the fasting-induced changes of several neuroendocrine axes (8), but this has not yet been directly studied in humans. Understanding the role of leptin in regulating neuroendocrine function during fasting in humans is a matter of profound physiologic interest. Moreover, this may have important therapeutic implications for low-leptin states, such as anorexia nervosa, hypothalamic amenorrhea, and lipoatrophy and may also elucidate the compensatory neuroendocrine mechanisms responsible for the plateauing effect of caloric restriction in the treatment of obesity.

To evaluate the role of leptin in regulating neuroendocrine and metabolic function during an acute fasting period, we studied eight healthy lean men under four

Received for publication November 27, 2002, and accepted in revised form March 6, 2003.

Address correspondence to: Christos S. Mantzoros, Division of Endocrinology, RN 325, Beth Israel Deaconess Medical Center, Harvard Medical School, 99 Brookline Avenue, Boston, Massachusetts 02215, USA. Phone: (617) 667-2151; Fax: (617) 667-2927; E-mail: cmantzor@caregroup.harvard.edu.

Conflict of interest: Christos S. Mantzoros has received research support and consulting fees from Amgen Inc.

Nonstandard abbreviations used: recombinant-methionyl human leptin (r-metHuLeptin); General Clinical Research Center (GCRC); triiodothyronine (T3); sex hormone–binding globulin (SHBG); thyroxine (T4); free thyroxine (FT4); reverse T3 (rT3); thyroxine-binding globulin (TBG); IGF-binding proteins (IGFBPs); plasma renin activity (PRA); luteinizing hormone (LH); thyrotropin-stimulating hormone (TSH); gonadotrophin-releasing hormone (GnRH); thyrotropin-releasing hormone (TRH); dual energy X-ray absorptiometry (DEXA); area under the curve (AUC); hypothalamic-pituitary-adrenal (HPA); sympathetic nervous system (SNS); resting metabolic rate (RMR); hypothalamic-pituitary-gonadal (HPG); hypothalamic-pituitary-thyroid (HPT); leptin receptor (ObR); signal transducer and activator of transcription-3 (STAT3); extracellular signal-regulated kinase (ERK); neuropeptide Y (NPY).