Selective capacity of metreleptin administration to reconstitute CD4$^+$ T-cell number in females with acquired hypoleptinemia

Giuseppe Matarese[a,b], Claudia La Rocca[a,b,1], Hyun-Seuk Moon[c,1], Joo Young Huh[c], Mary T. Brinkoetter[c], Sharon Chou[c], Francesco Perna[d], Dario Greco[e], Holly P. Kilim[c], Chuanyun Gao[c], Kalliope Arampatzi[c], Zhaoxi Wang[f], and Christos S. Mantzoros[c,g,2]

[a]Dipartimento di Medicina e Chirurgia, Università degli Studi di Salerno, Baronissi Campus, 84081 Baronissi Salerno, Italy; [b]Laboratorio di Immunologia, Istituto di Endocrinologia e Oncologia Sperimentale, Consiglio Nazionale delle Ricerche c/o Dipartimento di Biologia e Patologia Cellulare e Molecolare, and [d]Dipartimento di Medicina Clinica e Sperimentale, Università di Napoli Federico II, 80131 Napoli, Italy; [c]Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215; [e]Department of Biosciences and Nutrition, Karolinska Institutet, 14183 Huddinge, Stockholm, Sweden; [f]Harvard School of Public Health, Boston, MA 02115; and [g]Section of Endocrinology, Boston VA Healthcare System, Harvard Medical School, Boston, MA 02130

Edited by Philippa Marrack, Howard Hughes Medical Institute, National Jewish Health, Denver, CO, and approved December 19, 2012 (received for review August 24, 2012)

Leptin is an adipocyte-derived hormone that controls food intake and reproductive and immune functions in rodents. In uncontrolled human studies, low leptin levels are associated with impaired immune responses and reduced T-cell counts; however, the effects of leptin replacement on the adaptive immune system have not yet been reported in the context of randomized, controlled studies and/or in conditions of chronic acquired leptin deficiency. To address these questions, we performed a randomized, double-blinded, placebo-controlled trial of recombinant methionyl-human leptin (metreleptin) administration in replacement doses in women experiencing the female triad (hypothalamic amenorrhea) with acquired chronic hypoleptinemia induced by negative energy balance. Metreleptin restored both CD4$^+$ T-cell counts and their in vitro proliferative responses in these women. These changes were accompanied by a transcriptional signature in which genes relevant to cell survival and hormonal response were up-regulated, and apoptosis genes were down-regulated in circulating immune cells. We also observed that signaling pathways involved in cell growth/survival/proliferation, such as the STAT3, AMPK, mTOR, ERK1/2, and Akt pathways, were activated directly by acute in vivo metreleptin administration in peripheral blood mononuclear cells and CD4$^+$ T-cells both from subjects with chronic hypoleptinemia and from normoleptinemic, lean female subjects. Our data show that metreleptin administration, in doses that normalize circulating leptin levels, induces transcriptional changes, activates intracellular signaling pathways, and restores CD4$^+$ T-cell counts. Thus, metreleptin may prove to be a safe and effective therapy for selective CD4$^+$ T-cell immune reconstitution in hypoleptinemic states such as tuberculosis and HIV infection in which CD4$^+$ T cells are reduced.

CD4 cells | metabolism | nutritional status

Leptin is an adipocyte-derived hormone that conveys information on energy availability and whose circulating levels are proportionate to the amount of adipose tissue present (1). The functional long form of the leptin receptor (LepRb) is expressed in the hypothalamus where it regulates energy homeostasis and neuroendocrine function. It also is expressed in cells of the innate and adaptive immune system where leptin exerts key regulatory functions (2). On the basis of studies in rodents and observational and uncontrolled studies in a limited number of human subjects with congenital leptin deficiency, leptin has been proposed to act as a signal that conveys information on energy availability to the immune system. The immune system, like the neuroendocrine system, requires an adequate supply of energy for optimal functioning (3, 4). Evidence of leptin's importance can be found in animal studies in which mice lacking either leptin or LepRb show defects in cell-mediated proinflammatory T-helper 1 (Th1)-type immune responses (3, 4). Leptin stimulates in vitro the activation of monocytes from healthy humans in terms of reactive oxygen species production and chemotaxis in polymorphonuclear cells (2). Children with congenital leptin deficiency have reduced lymphocyte subpopulation numbers and show an increased risk for infection-related deaths during childhood. In these children, the T-cell CD4$^+$ fraction and the T-cell receptor (TCR)–specific proliferative responses are reduced as compared with the general population, and anti-CD3 and purified protein derivative (PPD) recall antigens stimulations were greatly impaired in these subjects (5). Very recent observational data show that impaired leptin signaling, secondary to a specific leptin-receptor polymorphism, is associated with reduced mucosal immunity against amebiasis in children (6). A direct effect of recombinant methionyl-human leptin (metreleptin) replacement to correct immunophenotypic changes, specifically increasing circulating naive CD4$^+$CD45RA$^+$ T-cell numbers and reversing impaired T-cell proliferation/cytokine release in response to TCR stimulation, has been observed in an extremely small, uncontrolled pilot study of children with congenital leptin deficiency (5). Treatment with metreleptin in these individuals also led to a switch from an anti-inflammatory Th2 cytokine secretion pattern to a predominantly proinflammatory Th1 phenotype.

Complete congenital leptin deficiency is an extremely rare condition. It has been described in only two families with high rates of consanguinity and in an additional two individuals with sporadic mutations of the leptin gene (1). Acquired leptin deficiency that develops in adulthood [as seen in states of negative energy balance such as malnutrition, HIV, or hypothalamic amenorrhea (HA)] is much more common than complete congenital leptin deficiency and occurs frequently when the balance

Author contributions: G.M. and C.S.M. designed research; G.M., C.L.R., H.-S.M., J.Y.H., M.T.B., S.C., F.P., D.G., H.P.K., C.G., K.A., and Z.W. performed research; C.L.R., H.-S.M., J.Y.H., M.T.B., S.C., F.P., D.G., H.P.K., C.G., K.A., and Z.W. analyzed data; and G.M. and C.S.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Data deposition: The data reported in this paper have been deposited in the Gene Expression Omnibus (GEO) database, www.ncbi.nlm.nih.gov/geo (accession no. GSE36990).

Clinical trial registration: clinicaltrials.gov registration nos. NCT00130117 and NTC01275053.

[1]C.L.R. and H.S.M. contributed equally to this work.

[2]To whom correspondence should be addressed. E-mail: cmantzor@bidmc.harvard.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1214554110/-/DCSupplemental.