

Volume 13, issue 2, June 2002 | Articles originaux

Interferon-alpha suppresses leptin levels: studies in interferon-alpha treated patients with hepatitis C virus infection and murine adipocytes

Abstract

Leptin is an adipocyte-derived protein, which signals the status of current energy stores and energy intake to the central nervous system. Interferon-alpha therapy is frequently associated with loss of appetite and weight reduction. In this study, we tested whether interferon-alpha is able to regulate leptin synthesis. We therefore determined leptin plasma concentrations in thirteen

patients with chronic hepatitis C who were treated with 1 x 107 IU interferon-alpha daily, up to 21 days after initial treatment. Furthermore, leptin concentrations and messenger RNA levels were quantified in interferon-alpha-treated and untreated murine adipocytes. After reaching peak plasma levels at 12 hours, probably reflecting the circadian rhythm, leptin concentrations fell and were significantly lower after 14 days. They remained significantly decreased 17 and 21 days after the start of the interferon-alpha treatment. In murine adipocytes exposed to interferon-alpha, leptin secretion was significantly decreased while messenger RNA levels remained unchanged. Our data suggest that, in contrast to proinflammatory cytokines such as interleukin-1, interferon-alpha suppresses leptin secretion in adipose tissue. We therefore hypothesize that loss of weight and appetite in interferon-alpha-treated patients with chronic hepatitis C might not be due to an elevation of leptin resulting in signals of increased energy stores in the brain.

Full text

INTRODUCTION

Hepatitis C virus infection is a major cause of chronic liver disease [1-3]. The clinical course seldom involves acute hepatitis, but commonly proceeds directly to chronic hepatitis, with the potential sequelae of cirrhosis and hepatocellular carcinoma. Interferon alpha (IFN-alpha) has proven clinical success in the treatment of hepatitis C virus infection [4, 5]. Currently, the detailed molecular mechanisms of action of IFN-alpha are insufficiently understood, but interactions with the cytokine cascade, as well as direct antiviral action might be involved in these mechanisms [6, 7]. IFN-alpha therapy is associated with a variety of side-effects. Besides influenza-like symptoms, aggravation of autoimmune disorders and effects on peripheral blood counts, loss of appetite and weight reduction is commonly observed.

Leptin, a 167-amino acid protein is one of the major factors in body weight control [8, 9]. This protein is produced by adipose tissue in proportion to fat mass and at low levels by other tissues such as skeletal muscle, placenta and stomach [10-12]. Leptin achieves most of its metabolic effects by interacting with specific receptors. The leptin receptor (obR) has five alternatively spliced forms; the long form of the receptor, which is primarily expressed in the hypothalamus, contains several motifs required for signal transduction,

whereas the other forms lack some or all of these motifs [13, 14]. Once released into the circulation it acts on the brain to inhibit food intake, stimulate thermogenesis and modulate various other physiological actions [15] including lipid metabolism [16], hematopoiesis [17], pancreatic beta-cell and ovarian function [12]. Leptin-deficient *(ob/ob)* mice display low body temperature, hyperphagia, decreased energy expenditure, decreased immune function and infertility [12]. Feeding, glucocorticoids, insulin and obesity [8] as well as cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 (IL-1) [8, 18-20] are assumed to induce leptin expression while fasting, beta-receptor agonists, cAMP and thiazolidinediones [8, 21-23] suppress leptin expression. Furthermore, leptin is produced during the acute phase response [24].

In the present study, we tested whether IFN-alpha is able to regulate leptin synthesis *in vivo* and *in vitro*. Leptin levels were determined before and after treatment with IFN-alpha in patients with chronic HCV infection. In additional experiments, direct effects of IFN-alpha on leptin were tested in differentiated murine adipocytes (3T3-L1 preadipocytes).

METHODS

Clinical study (Table 1)

Thirteen patients with chronic hepatitis C who underwent daily treatment with 1 x 10^7 IU IFN-alpha participated in this study. All patients had a body mass index (BMI) between 19 and 25 kg/m^2. Appetite and BMI remained unchanged during the observed time period. None of the tested subjects suffered from endocrine disorders including diabetes mellitus.

Venous peripheral blood was drawn from the 13 subjects before IFN-alpha treatment (8 am) and 2, 6, 12, 24, 48, 72 hours, 7, 10, 14, 17 and 21 days, respectively, after the start of IFN-alpha treatment. Blood was collected into EDTA tubes and centrifuged at 2,200 g for 10 min. Plasma was stored at - 80° C until assayed. Leptin concentration was determined by a commercially available enzyme-linked immunosorbent assay using two monoclonal anti-leptin-antibodies (R&D Systems, Wiesbaden, Germany).

Informed consent was obtained from all participating subjects. Procedures were performed in accordance with institutional guidelines.

Cell culture

Murine preadipocyte 3T3-L1 cells (ATCC, Manassas, VA, USA) were maintained in culture flasks at 37° C and at 5% CO_2/95% air in Dulbecco´s modified Eagle´s medium (DMEM, Life Technologies, Rockville, MD, USA) supplemented with 10% fetal bovine serum (Life Technologies) and 10 mug/ml penicillin/streptomycin (Seromed, Berlin, Germany). Fresh medium was added every third day and cells were split at a 1:5 ratio every 7 days. 3T3-L1 preadipocytes were differentiated into adipocytes as described previously [25]. Briefly, confluent cells were differentiated into adipocytes by adding 250 nM dexamethasone (Sigma, St. Louis, MO, USA), 1 mug/ml bovine insulin (Sigma) and 500 nM 1-methyl-3-isobutylxanthine (ICN, Costa Mesa, CA, USA) for 2 days. 3T3-L1 preadipocytes were maintained in DMEM medium for 8-10 additional days. Fully-differentiated 3T3-L1 adipocytes, 10-12 days after induction of differentiation, were switched to fresh medium before addition of murine IFN-alpha (ICN, Costa Mesa, CA, USA).

Murine leptin measurement

Murine leptin concentrations were determined by enzyme-linked immunosorbent assay (R&D Systems) in supernatants of fully-differentiated 3T3-L1 adipocytes stimulated with IFN-alpha as indicated. To control for cell counts, cells of each well were lysed with 0.1 M NaOH and cell protein was determined by the Lowry method [26].

Reverse transcription (RT) and polymerase chain reaction (PCR)

Murine leptin cDNA for Northern analysis was obtained by specific RT-PCR. Reverse transcription was performed from mRNA of murine adipose tissue by Superscript II reverse transcriptase (Life Technologies), using a random hexanucleotide mix (Roche, Basel, Switzerland). Murine leptin cDNA-PCR was performed with Hot Star Taq Polymerase (Qiagen, Valencia, CA, USA) using 10 mM dNTPs (Amresco, Solon, OH, USA), 15 pmol of each sense and antisense primer in 30 cycles of 96° C, 54° C and 72° C, 1 min each, in a total volume of 50

mul. For murine leptin cDNA - PCR 5'-ACT TCA TTC CTG GGC TTC AC-3' and 5'-GCT CTT ATC TCT ACT TGC TG-3' primers were used.

RNA preparation and Northern analysis

Total RNA from murine adipose tissue and 3T3-L1 adipocytes, respectively, was extracted using the RNA-Clean System (Dipro, Wiener Neudorf, Austria). Ten microgram of total RNA were separated by denaturating agarose gel electrophoresis, blotted onto nylon membranes (Duralon-UV membrane, Stratagene, La Jolla, CA, USA) and hybridized with radiolabeled murine leptin cDNA as described [27]. Control hybridization was performed with rat GAPDH cDNA. The amount of murine leptin and GAPDH mRNA was evaluated by PhospholmagerTM (Cyclone, Packard, Meriden, CT) using Optiquant (Packard) software.

Statistical analysis

Data are expressed as means ± SEM. Statistical differences between human leptin concentrations before and after IFN-alpha treatment, as well as between means of murine leptin concentrations were estimated by the paired t-test. Statistical significance was inferred at a two-tailed p-value < 0.05. SPSS for Windows (Version 8.0) was used for statistical analyses.

RESULTS

Clinical study

Leptin concentrations were measured before and 2, 6, 12, 24, 48, 72 hours, 7, 10, 14, 17 and 21 days, respectively, after the start of IFN-alpha treatment in plasma of 13 HCV patients. As shown in Figure 1 leptin concentrations tended to increase up to 12 hours after the start of IFN-alpha treatment. After 12 hours, leptin concentrations were significantly higher when compared to baseline levels (12 hours: 11.32 ± 2.78 ng/ml *versus* 6.76 ± 1.26 ng/ml before IFN-alpha treatment; p = 0.02). Leptin concentrations tended to decrease after reaching a peak level 12 hours after initial IFN-alpha treatment. Fourteen days after start of IFN-alpha treatment, leptin concentrations were significantly lower when compared to baseline levels (14 days: 5.79 ± 1.31 ng/ml *versus* 6.76 ± 1.26 ng/ml before IFN-alpha treatment; p= 0.04), and remained significantly lower after 17 days and 21

days, respectively (17 days: 5.49 ± 1.34 ng/ml (p = 0.02); 21 days: 4.95 ± 0.88 ng/ml (p = 0.05)).

Leptin concentrations did not differ significantly between female and male patients (data not shown).

Leptin secretion in murine adipocytes

Leptin concentrations were measured in supernatants of untreated cells and cells treated with 10 IU/ml, 100 IU/ml and 1,000 IU/ml IFN-alpha after 12, 18, 24 and 40 hours, respectively. Leptin concentrations in supernatants of untreated 3T3-L1 adipocytes increased from 33.3 ± 3.8 pg/ml after 12 hours to 118 ± 3.2 pg/ml after 40 hours. Dose-dependent suppressive effects of IFN-alpha on leptin concentrations in the cell supernatant of 3T3-L1 adipocytes are shown in Figure 2. At the highest indicated IFN-alpha concentration of 1,000 IU/ml leptin levels were decreased by 43 ± 4% after 12 hours (p = 0.04), by 33 ± 5% (p = 0.05) after 18 hours, by 34 ± 1% after 24 hours (p = 0.02) and by 29 ± 3% after 40 hours (p = 0.05).

Northern analysis

Messenger (m)-RNA of 3T3-L1 adipocytes was isolated after incubation times of 6, 12, 18, 24 and 40 hours in untreated cells and in cells exposed to murine IFN-alpha at concentrations of 10 IU/ml, 100 IU/ml and 1,000 IU/ml, respectively. Northern blot analysis showed no difference in m-RNA levels of murine leptin after IFN-alpha exposure at any concentration or any exposure time (Figure 3).

DISCUSSION

Leptin is an adipocyte-derived hormone, that structurally belongs to the long-chain helical cytokine family. This cytokine represents an important link between fat mass on the one hand and the regulation of energy balance on the other.

In mice, high leptin levels cause weight loss by suppressing food intake and increasing motor activity, energy metabolism and oxygen consumption [28].

Weight loss and decrease in appetite is a common side effect of IFN-alpha treatment. In this study we tested the influence of IFN-alpha on leptin in 13

patients with chronic hepatitis C. Leptin concentrations were slightly increased up to 48 hours after IFN-alpha treatment. After 48 hours indeed, leptin concentrations in plasma fell and were significantly lower after 14 days and remained significantly decreased after 17 days and 21 days, respectively, when compared to baseline levels. To test whether these alterations in leptin concentrations were directly induced by IFN-alpha, we tested the influence of IFN-alpha on leptin secretion in cell culture. As adipocytes are the major source of circulating leptin, we chose the murine 3T3-L1 adipocyte cell line for our experiments. Our *in vitro* results suggest a direct, suppressive effect of murine IFN-alpha on leptin secretion in 3T3-L1 adipocytes. Similarly, leptin mRNA levels in IFN-alpha-treated as well as in untreated 3T3-L1 adipocytes suggest a post-transcriptional effect of IFN-alpha or an increased turnover of leptin. When extrapolated to the *in vivo* situation, our *in vitro* results suggest that suppression of leptin levels is a long term, direct effect of IFN-alpha. The significantly increased leptin concentration observed 12 hours after the start of IFN-alpha treatment might be interpreted as a consequence of the circadian rhythm of leptin, as Sinha *et al.* [29] reported that leptin secretion is characterized by a nocturnal rise which might be responsible for appetite suppression while sleeping. Additionally, it might be suggested that initially increased leptin levels could be due to indirect effects of IFN-alpha treatment, such as regulation of cytokine synthesis by the IFN-alpha.

What would be the consequences of decreased leptin levels in IFN-alpha-treated HCV patients? Low leptin levels are thought to lead to a state in which food intake exceeds energy expenditure. Our results therefore suggest that IFN-alpha induced weight loss might not be due to leptin-induced, false signalling of excess energy stores to the brain.

Other adaptive changes include promotion of intracellular lipid concentrations by increasing fatty-acid and triglyceride synthesis and concomitantly increasing lipid oxidation.

Furthermore, low leptin levels result in the reduction of thyroid and gonadal hormones as well as the activation of the hypothalamic-pituitary-adrenal axis leading to increased release of glucocorticoids [8, 30]. Besides weight loss, thyroid dysfunction is also a common side-effect of IFN-alpha treatment in chronic hepatitis C patients [31]. Considering the association between leptin plasma concentrations and thyroid hormone levels it seems conceivable that

decreased leptin levels in IFN-alpha-treated patients could partly be responsible for the thyroid dysfunction often observed in these patients.

Liver disease is often associated with glucose intolerance and hyperinsulinemia [32]. Effects of leptin on insulin release from isolated pancreatic islets, perfused pancreas, or insulin-secreting cell lines were reported to be stimulatory or inhibitory [30]. Although findings about the effects of leptin on insulin release from isolated pancreatic islets, perfused pancreas, or insulin-secreting cell lines were reported to be stimulatory or inhibitory [30] and, thus contradictory, it is conceivable that long term suppressive effects of IFN-alpha on leptin concentrations affect glucose metabolism in patients with chronic HCV infection.

Interestingly, interleukin-1, a proinflammatory cytokine [6], stimulates leptin expression [18], while partially antiinflammatory acting IFN-alpha decreases leptin levels, suggesting a contrary effect of proinflammatory and antiinflammatory cytokines on leptin levels.

CONCLUSION

In conclusion, we found that leptin concentrations are decreased in IFN-alpha treated HCV patients. *In vitro* IFN-alpha has a direct, suppressive effect on leptin secretion by murine adipocytes. We therefore hypothesize that weight loss in IFN-alpha-treated HCV patients might not be due to improperly high levels of leptin signalling an excess of energy.

Acknowledgement. This work was supported by grant P 11693-Med of the Austrian Science Fund (to JRP), by grant Nr. 6442 of the Austrian Nationalbank (to JRP) and by grant 14641-Med of the Austrian Science Fund (to HT).

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Figures

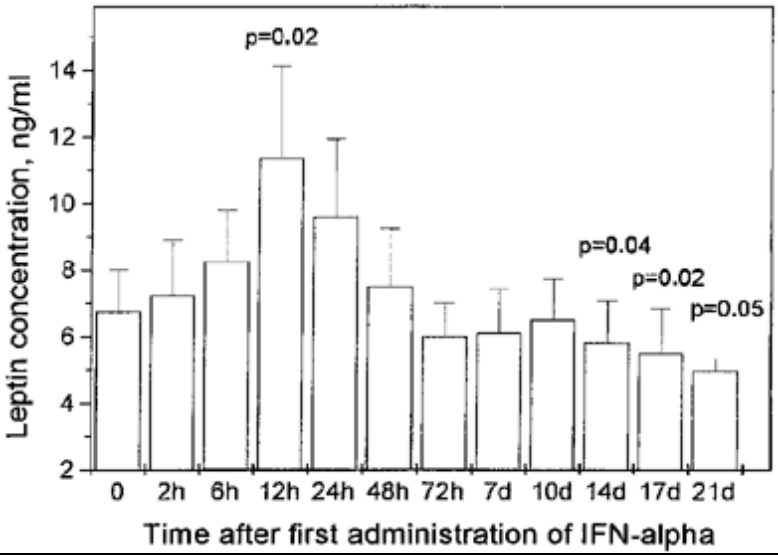


Figure 1

Leptin plasma levels during IFN-alpha treatment.

1 x 10^7 IU IFN-alpha were administered subcutaneously, daily to 13 patients with chronic hepatitis C. Leptin concentrations reached peak values after 12 h (p = 0.02) probably reflecting the circadian rhythm, and were significantly lower after 14 days (p = 0.04), 17 days (p = 0.02), and 21 days (p = 0.05), respectively, when compared to baseline leptin concentrations. Means ± SEM.

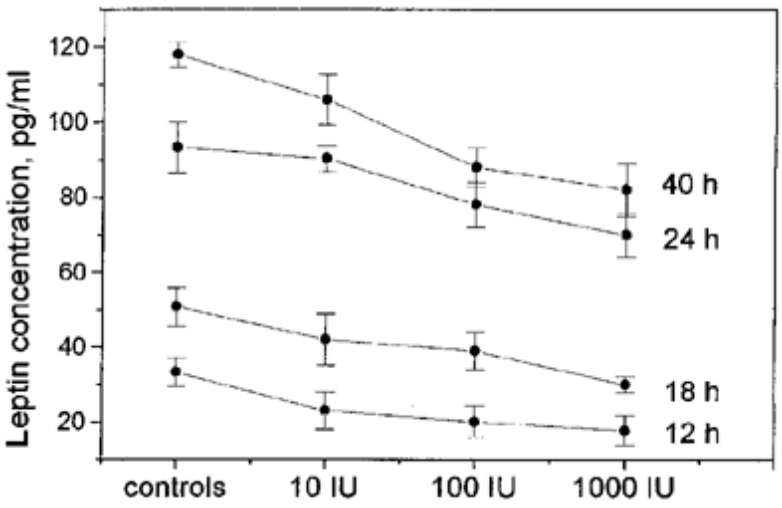


Figure 2

Influence of murine IFN-alpha on leptin secretion in murine adipocytes.

3T3-L1 adipocytes were exposed to IFN-alpha at concentrations of 10 IU/ml, 100 IU/ml and 1,000 IU/ml. Leptin concentrations were measured in the supernatant of treated and untreated cells 12, 18, 24, and 40 hours after exposure.

Leptin concentrations decreased significantly in a dose-dependent fashion at all exposure times. Differences between untreated and treated cells were significant ($p < 0.05$) at any exposure time. Decreases in leptin concentrations were statistically significant at all concentrations and all exposure times except at a concentration of 10 IU IFN-alpha after 40 hours. Data reflect 3 independent experiments.

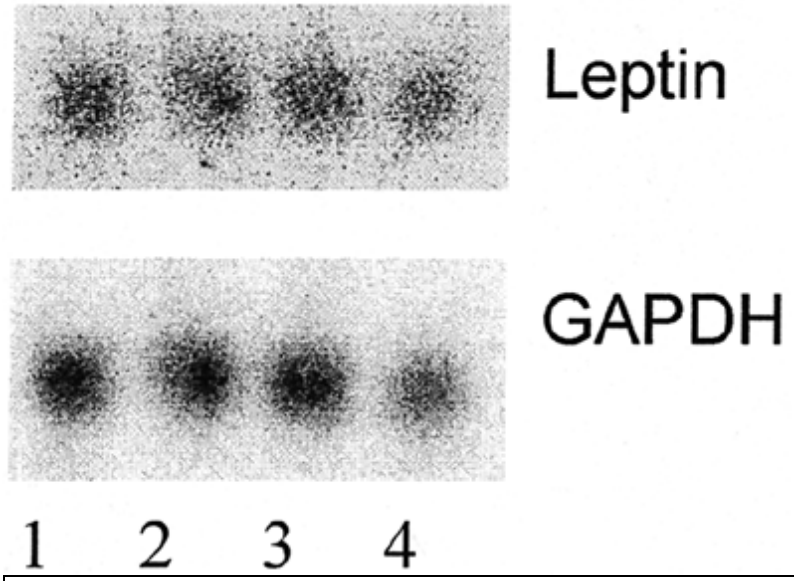


Figure 3

Northern analysis.

Total RNA was extracted from 3T3-L1 adipocytes after 6 hours exposure to IFN-alpha (lanes 2-4), and from untreated 3T3-L1 adipocytes (lane 1) as indicated. Equal loading was ascertained by hybridization with the housekeeping gene glyceraldehyde-3-phophate dehydrogenase (GAPDH).

Table 1
Clinical characteristics of HCV patients included in the study

	Female HCV patients (n = 4)	Male HCV patients (n = 9)
Age, years	36 ± 13	32 ± 6
Height, m	172 ± 9	182 ± 7
Weight, kg	64 ± 7	77 ± 9
BMI, kg/m²	24 ± 1	22 ± 4
AST, U/l	24 ± 19	31 ± 17
ALT, U/l	35 ± 27	76 ± 48
Bilirubin, mg/dl	0.70 ± 0.47	0.58 ± 0.08
PT, %	98 ± 4	110 ± 11

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