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Cerebrospinal Fluid and Plasma Leptin Measurements: Covariability with Dopamine and Cortisol in Fasting Humans*

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ABSTRACT

Leptin (OB protein) is an important signal in the regulation of energy balance. Leptin levels correlate with adiposity, but also decrease acutely with caloric restriction and increase with refeeding. The brain is an established critical site of leptin function, yet little is known about leptin concentrations in the central nervous system relative to plasma levels, psychiatric diagnoses, and other endocrine parameters. Therefore, using a novel ultrasensitive leptin assay, we explored relationships of human plasma and cerebrospinal fluid (CSF) leptin levels to body mass index, smoking, posttraumatic stress disorder diagnosis, and levels of dopamine, monoamine metabolites, β-lipotropin, glucocorticoid, and thyroid and cytokine hormones. A strong linear relation between CSF and plasma leptin levels in the am ($r = 0.63$; $P < 0.002$) and afternoon ($r = 0.90$; $P < 0.0001$) was revealed. CSF and plasma leptin concentrations decreased during a 12- to 20-h period of fasting. A strong association was found between plasma leptin and CSF dopamine levels ($r = 0.74$; $P < 0.01$) as well as between CSF leptin levels and urinary free cortisol ($r = 0.73$; $P < 0.01$). Both of these parameters covaried with leptin independently of adiposity, as estimated by body mass index. Implications for leptin transport, regulation, and its potential role in therapeutic strategies for obesity and diabetes are discussed. (*J Clin Endocrinol Metab* **84:** 3579–3585, 1999)

THE ADIPOCYTE-SECRETED hormone leptin is implicated in the regulation of energy homeostasis as a protein that signals the central nervous system (CNS) to decrease food intake and adiposity (1). Leptin is secreted in proportion to the amount of adipose tissue (2, 3) and exhibits a diurnal pattern of peak concentrations at night that are related to insulin responses to meals (4, 5). Accordingly, leptin concentrations have been shown to decrease in response to fasting or energy restriction and increase after refeeding (6–8). Decreases in circulating leptin are related to increased sensations of hunger during energy restriction in humans (9). Rodents (10–12) and humans (13, 14) with homozygous mutations in the leptin or leptin receptor genes manifest hyperphagia and obesity. In rodents, central administration of leptin decreases food intake and body weight (15–17) and increases energy expenditure (18). Central infusion of leptin also decreases food intake while activating the sympathetic nervous system in nonhuman primates (19). Activation of leptin receptors throughout the hypothalamus is believed to be critical for these anorectic effects (20–22).

In humans, cerebrospinal fluid (CSF) and circulating peripheral levels of leptin are positively correlated (1, 23, 24). However, in individuals with high levels of circulating leptin (and high levels of body fat), the CSF to plasma concentration ratio is lower than that in nonobese individuals (1, 24). This finding subsequently led to investigations into the transport mechanisms of leptin uptake, mechanisms that may be compromised in obesity. These are hypothesized to include saturable receptor binding at the blood-brain barrier (1, 25), decreased transport via receptor binding at the choroid plexus (26), or nonsaturable diffusion (24).

Despite evidence that the brain is a critical site of leptin action, a paucity of data exist on human CSF leptin, particularly in terms of its relationship with other neural and endocrine variables and how they may correlate over time. One exception is a study that assessed relationships between CSF and serum leptin levels and CSF and serum levels of neuropeptide Y. Covariability between leptin and neuropeptide Y was not found (23).

Although single datum point CSF samples of leptin have helped shed light on the nature of this hormone's transport into the CNS (1, 24), serial sampling of CSF in humans via a flexible, indwelling catheter may have significant advan-

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tages over one-time CSF sampling (27–29). We now extend the use of this repeated CSF-sampling technique to explore covariability of CSF leptin concentrations, not only with plasma leptin levels, but with other bioactive substances not previously examined in relationship to CSF leptin.

Specifically, morning (am) and evening (pm) CSF and blood samples were collected from male participants and variously assayed for leptin, dopamine, dopamine and serotonin metabolites, CRH, interleukin-6 (IL-6), immunoreactive β-lipotropin (irβ-lipotropin), and thyroid hormones. Urinary free cortisol (UFC) excretion was measured over a 24-h period. In addition to these neuroendocrine variables, covariabilities between these substances and leptin levels were examined as a function of diurnal phase, body mass index (BMI), tobacco smoking, and medical diagnosis of posttraumatic stress disorder (PTSD).

Materials and Methods

Participants

Approval for the study was obtained from the institutional review board of the University of Cincinnati Medical Center and the Veterans Affairs Medical Center (Cincinnati, OH). Informed consent from each patient or volunteer was obtained before their participation. The participants were all men between 23–50 yr of age. Ten were combat veterans meeting the DSM-IV criteria (30) for PTSD but with no other medical problems. Seven of these patients had been taking prescribed antidepressants, but abstained from them for at least 2 weeks or five disappearance half-lives before the study. Ten additional volunteers were age-matched healthy men with no history of substance abuse or other psychiatric illness and no first degree relatives with these conditions. Before the study each participant underwent standard physical, blood, and urine tests to rule out abnormalities.

CSF, plasma, and urine collection

On the evening before the study, participants ate a standard 666-cal meal (20% protein, 24% fat, and 56% carbohydrate) and fasted for approximately 12 h before insertion of a 20-g Teflon indwelling lumbar catheter as previously described (28) except that subjects were placed in the seated position. The catheter was advanced 5–15 cm cephalad into the subarachnoid space and was secured from 0800–1700 h while CSF was collected into iced test tubes at a rate of 0.1 mL/min from a Tygon tube extension attached to a peristaltic pump. Physiological saline solution was infused at 100 mL/h throughout the procedure through an antecubital vein. Blood was withdrawn every half-hour from an indwelling venous catheter, and all urine was collected. No smoking or oral intake was permitted during the study. Participants were confined to bed rest beginning the midnight before CSF sampling.

Sensitive human leptin assay

A new RIA was developed to sensitively measure low levels of human leptin in CSF, serum, plasma, or culture medium samples (Linco Research, Inc., St. Charles, MO). The assay used a polyclonal antibody raised in rabbits against highly purified recombinant human leptin. Calibrators (0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, and 10.0 ng/mL) and ^{125}I-labeled tracer were prepared with recombinant human leptin. Calibrators (100 μL) or CSF and plasma specimens (25–100 μL) in duplicate were mixed with antibody (100 μL) and incubated overnight (20–24 h) at room temperature. If the specimen volume was less than 100 μL, the remaining volume was adjusted with assay buffer. [^{125}I]Leptin (100 μL) was added, and the samples were mixed and then incubated for an additional 20–24 h at room temperature. One milliliter of cold (4 C) precipitating reagent (antirabbit rabbit IgG) was added to all tubes (except total count tubes) to precipitate the antibody-antigen complex. Tubes were centrifuged at 4 C for 20 min at 2500 × *g*. The supernatants were decanted, and the pellets were counted to determine bound radioactivity. Calculation of unknown leptin concentrations in samples was performed by log-logit transformation. Coefficients of variation at leptin concentrations between 0.44–4.24 ng/mL ranged from 3.74–7.28% within runs and from 3.24–8.90% between runs.

Recovery of different amounts (range, 0.2–2.0 ng/mL) of recombinant human leptin to added human serum averaged 104–118%. Linear dilution of four pooled human serum samples with concentrations ranging from approximately 1.1–4.2 ng/mL was assessed by measuring each five times at volumes of 100, 75, 50, and 25 μL after dilution with assay buffer. Values of 97 ± 2%, 93 ± 5%, and 81 ± 6% of the measured concentrations at 100 μL were measured at 75, 50, and 25 μl, respectively. Concentrations of leptin in human serum measured with the new sensitive RIA (catalogue no. SHL-81K) were very similar, with a slope close to 1.0 ($y = 1.04x + 0.68$), and were highly correlated (r = 0.985) with concentrations determined with the standard human leptin RIA (catalogue no. HL-81K) (31).

Monoamine and hormone assays

CSF samples were also assayed for dopamine (picomoles per mL), the dopamine metabolite homovanillic acid (HVA; picomoles per mL), the serotonin metabolite 5-hydroxyindoleacetic acid (5HIAA; picomoles per mL), the cytokine IL-6 (picograms per mL), CRH (picograms per mL), and irβ-lipotropin (picograms per mL). Plasma samples were also assayed for 5HIAA, TSH (microinternational units per mL), total T_3 (TT_3; nanograms per dL), T_4 (nanograms per dL), HVA, and IL-6. Urine samples were collected for analysis of UFC (micrograms per 24 h).

Dopamine, HVA, and 5HIAA were assayed via HPLC with an electrochemical detection as described previously (29). IL-6 was quantified with a commercial enzyme-linked immunosorbent assay kit (Endogen, Inc., Woburn, MA), using sets of paired monoclonal antibodies for capture and detection. The mean inter- and intraassay coefficients of variation for the control phase were less than 10%, and the detection limit was less than 1 pg/mL. RIAs, with the modifications described previously, were used to quantify CRH (28) and irβ-lipotropin (27). TSH, TT_3, and T_4 in blood and UFC were assayed by standard thyroid and free cortisol profiles at the Veterans Affairs Clinical Laboratory in Cincinnati.

Statistical analysis

ANOVA was used to assess differences between leptin levels and dichotomous variables, including clinical diagnosis and cigarette smoking. Paired *t* tests were used to assess differences between am and pm leptin levels within participants. Leptin values were regressed on behavioral and neuroendocrine variables. Partial correlation coefficients were obtained on variables found to be associated with leptin levels to control for potential confounds. When not normally distributed, data were logarithmically transformed for the best description of relationships and omitted if outside of 3 SD. BMI was calculated as weight in kilograms divided by height in meters squared. Data represent the mean ± SEM. Except for CRH and IL-6, for which one am and one pm sample each were analyzed, values entered into the analyses for all other biological variables represent the mean concentrations of samples collected at regular intervals from 1100–1700 h. Significance levels for two-tailed tests (except for one-tailed where noted) were set at $P < 0.05$.

Results

Relationship among leptin levels, medical diagnosis, and cigarette smoking

No significant differences were found in CSF and plasma leptin concentrations between the PTSD and normal volunteer groups. Therefore, data from all participants were treated collectively in the analysis of leptin results. Cigarette smokers and nonsmokers could not be differentiated on the basis of CSF or plasma leptin levels, but were better predicted by a decrease in the CSF concentration of HVA and an increase in the plasma concentration of 5HIAA (r = −0.696; $P < 0.001$ and r = 0.487; $P < 0.035$, respectively), as previously reported (32).

Relationship between leptin levels and BMI

The mean BMI of the participants was 27.0 ± 1.0 kg/m^2 (range, 18.9–35.8). BMI was positively associated with am CSF (r = 0.42; $P < 0.03$), pm CSF (r = 0.62; $P < 0.01$), am plasma (r = 0.62; $P < 0.01$), and pm plasma leptin levels (r = 0.68; $P < 0.01$). Thus, 18–46% of the variance in leptin levels could be explained by differences in BMI.

Relationships between CSF and plasma leptin levels

Mean plasma leptin concentrations were lower in the pm (3.6 ± 0.5 ng/mL) than in the am (4.6 ± 0.7 ng/mL; $P < 0.01$), and were strongly correlated with each other (r = 0.90; $P < 0.001$). CSF leptin levels, also, decreased significantly from am (0.07 ± 0.02 ng/mL) to pm (0.047 ± 0.01 ng/mL; $P < 0.05$) and were strongly correlated with each other (r = 0.85; $P < 0.001$). As depicted in Fig. 1A, am CSF and plasma leptin concentrations were positively related (r = 0.63; $P < 0.002$). Figure 1B shows that this relationship was stronger toward late afternoon (r = 0.88; $P < 0.001$). In addition and as shown in Fig. 1C, am plasma levels of leptin were highly predictive of afternoon leptin levels in the CSF (r = 0.85; $P < 0.001$).

Analysis of CSF/plasma leptin ratios

The CSF/plasma ratio was used as an indicator of the efficiency of adipose-secreted leptin transport into the brain. As shown in Fig. 2A there was a positive correlation between the CSF/plasma ratio and plasma leptin levels (r = 0.51; $P < 0.01$) in the am. As depicted in Fig. 2B, after additional time without food (pm samples) the positive correlation between CSF/plasma ratio and plasma leptin levels was stronger (r = 0.56; $P < 0.005$). As expected, BMI, which was strongly correlated with plasma leptin levels, was found to similarly correlate with the CSF/plasma ratio.

Relationship between leptin and neuroendocrine variables

As shown in Table 1, simple regression coefficients for leptin levels regressed on various neuroendocrine variables yielded significant associations with dopamine, UFC, TT_3, and irβ-lipotropin. Because BMI was significantly interrelated with several of the biological variables, partial correlations controlling for BMI were obtained from these significant leptin-neuroendocrine relationships.

The effect of partialing out variance due to BMI is shown in Table 2. As a result of these analyses, levels of plasma TT_3 and CSF irβ-lipotropin were found to covary mostly as a function of BMI and not leptin. CSF dopamine levels were found to covary with plasma leptin levels. Twenty-four-hour UFC excretion was significantly associated with CSF leptin and marginally with am plasma leptin concentrations. Both of these relationships were significant after controlling for BMI.

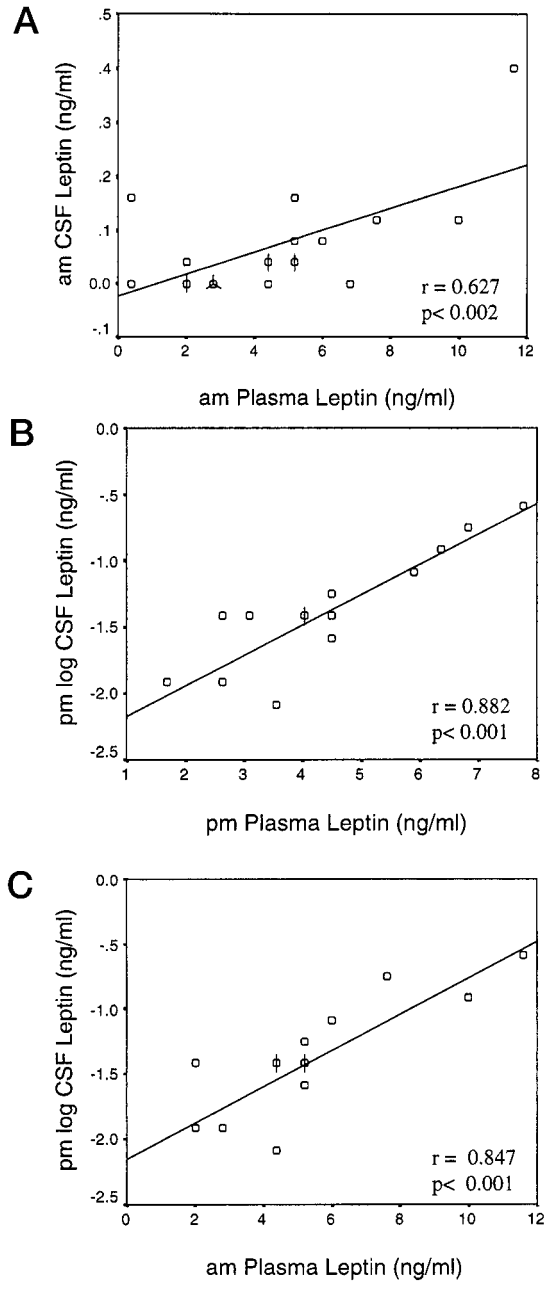

FIG. 1. A, Relationship between the mean am leptin level in plasma and CSF of all participants (n = 20). B, Relationship between the mean pm leptin level in plasma and CSF of all participants (n = 20). C, Relationship between the mean am leptin level in blood and the pm leptin level in CSF of all participants (n = 20). *Strikes through open circles* represent overlapping data from more than one participant.

Discussion

This study examined concentrations of leptin in plasma and CSF across time and with levels of other plasma- and brain-derived neuroendocrine substances in humans. CSF and blood samples were taken from volunteers who had fasted for 12 h when the first samples were taken and for an additional 8 h when the last samples were obtained. We were able, therefore, to explore covariability in the concentrations of these neuroendocrine substances against a background of increasing duration of fasting in individuals with a range of body fat mass.

Our results confirm the existence of a strong linear relationship between CSF and plasma leptin levels as has been reported in previous studies (23, 24). Additionally, we found this relationship to grow stronger toward evening, as participants approached 20 h of fasting and when mean con-

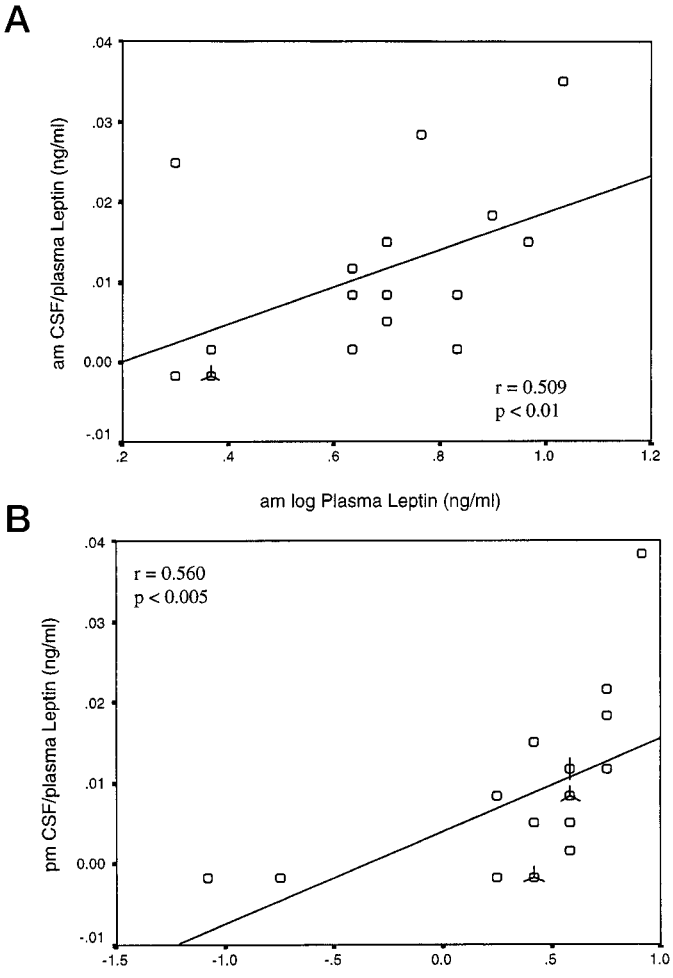

FIG. 2. A, Correlations between the mean am CSF/plasma leptin ratio and concentration of am plasma leptin (n = 18). B, Correlations between the mean pm CSF/plasma ratio and concentration of pm plasma leptin (n = 20). *Strikes through open circles* represent overlapping data from more than one individual.

centrations of both plasma and CSF leptin decreased. This observed pattern is also consistent with prior reports of decreases in plasma leptin concentrations with caloric restriction (6–9), and extends them by showing that CNS leptin levels also decrease under these conditions. Decreased adipocyte glucose metabolism resulting from a lowering of circulating insulin levels during the caloric deficit would result in a decrease in leptin production (33). Decreased leptin levels in CNS are likely to be a direct result of attenuated leptin transport into the CNS due to lower plasma leptin levels.

CSF/plasma leptin ratios were examined as a function of the amount of plasma leptin present (or BMI), and as a function of caloric restriction. In the am, following an overnight fast (12 h without food), high plasma leptin concentrations were associated with high CSF/plasma leptin ratios. This pattern is different from that observed by Schwartz *et al.* (22), Caro *et al.* (1), and Dotsch *et al.* (23), where in participants who similarly fasted overnight, there was a negative correlation between their CSF/plasma leptin ratios and plasma leptin. The pattern of decreased CSF/plasma concentrations with increasing plasma leptin concentrations (and increasing BMI) has been interpreted in terms of a leptin transport system that becomes saturated in the presence of higher levels of plasma leptin (1, 24–26).

An explanation for the observed differences in the patterns of CSF/plasma ratios may be due to differences in BMI ranges between the studies. The mean BMIs for the three subgroups in the study by Schwartz *et al.* (22) were reported to be between 22.9–24.9 (the heaviest quantile of the entire groups was 26.1 ± 0.6). Participants in the study by Dotsch *et al.* (23) were all lean and of average weight. In sharp contrast, 78% of our group ranged in BMI from 26.2–35.8. In the study by Caro *et al.* (1), the subjects included obese participants (mean BMI, 31.7), but six of eight of the individuals were women. Serum leptin levels have been shown to be consistently higher in women than in men (24, 34) before and after restriction (7), whereas CSF concentrations have been found not to differ (35). Higher plasma levels would be expected to yield smaller CSF/plasma ratio values, possibly shifting a positive correlation to a negative one.

Our results with an all-male group that included overweight and obese individuals with high BMIs do not support the hypothesis that CSF leptin transport is attenuated with increasing plasma leptin (and BMI). Analysis revealed higher, not lower, CSF/plasma ratios with increasing plasma leptin. CSF leptin transport as a function of peripheral leptin concentrations may, therefore, be more accurately described as an inverted U function with possibly an alternate transport mechanism acting in response to excessive plasma leptin such as occurs in obesity. Caro *et al.* (1) proposed that perhaps very high levels of plasma leptin may be sufficient to increase leptin transport into the CNS. They noted the unusual case of a patient with unusually high serum leptin levels who showed a lean pattern of correspondingly high CSF leptin level. This case, although probably atypical, would be consistent with a hypothesized U-shaped function of leptin transport. Certainly, additional studies with individuals falling within a large range of BMIs and in which females and males are analyzed separately would be needed to provide support for this alternate hypothesis.

Unique to the present study is that leptin was assayed in the same individuals a second time, after further restriction from food intake (for a total of 20 h). At this time, the positive association between plasma leptin levels and CSF/plasma leptin ratios was strengthened. Plasma leptin levels declined from the first sampling, as would be expected with further energy restriction (6–8). Within certain limits, plasma leptin during caloric restriction may be more efficiently transported into brain via an unsaturated transport mechanism. Such high CSF/plasma ratios with low plasma leptin would represent the left curve of an inverted U function. Consistent with this idea, patients with anorexia nervosa who have low levels of plasma leptin concurrent with their low body fat content and restricted energy intake were found to have high CSF/plasma leptin ratios (36).

Another goal of this study was to explore the relationship between CSF and plasma leptin levels with psychiatric diagnoses (tobacco dependence and PTSD) and several neuroendocrine variables not previously studied in relationship

TABLE 1. Pearson correlation coefficients for neuroendocrine variables

Variables	am CSF leptin	pm CSF leptin	am P leptin	pm P leptin
CSF-derived				
Dopamine	0.250	0.433[a]	0.464[a]	0.583[b]
HVA	−0.126	0.046	−0.013	0.078
DA:HVA	0.196	0.147	0.282	0.214
5HIAA	0.166	0.319	0.297	0.316
5HIAA:HVA	0.316	0.205	0.406	0.206
irβ-lipotropin	0.322	(0.428[a])	(0.417[a])	(0.417[a])
IL-6 (am)	−0.225	−0.258	0.039	−0.184
IL-6 (pm)	0.167	0.176	0.212	0.025
TSH	−0.215	−0.207	−0.117	−0.214
TT_3	−0.131	−0.280	−0.532[a]	−0.516[a]
T_4	0.297	0.248	0.139	0.047
Plasma-derived				
HVA	−0.083	−0.088	0.054	−0.050
5HIAA	0.243	0.078	0.297	0.224
CRH (am)	0.020	−0.062	0.203	0.153
CRH (pm)	0.028	0.060	0.054	0.035
IL-6 (am)	0.129	0.269	0.270	0.345
IL-6 (pm)	0.119	0.267	0.271	0.350
Urine				
UFC	0.773[b]	0.768[b]	0.638[b]	0.556[a]

All tests of significance were two-tailed except those in *parentheses*, which indicate one-tailed significance.
[a] $P < 0.05$.
[b] $P < 0.01$.

TABLE 2. Simple and partial correlation coefficients between leptin and neuroendocrine variables after controlling for BMI

Dependent variable	Independent variable	r[a]	pr	*P*
CSF leptin (am)	UFC	0.773	0.735	<0.01
CSF leptin (pm)	Dopamine	0.433	0.362	NS
	irβ-lipotropin	0.428	0.170	NS
	UFC	0.768	0.661	<0.01
Plasma leptin (am)	Dopamine	0.464	0.728	<0.01
	irβ-lipotropin	0.417	0.149	NS
	TT3	−0.532	−0.032	NS
	UFC	0.638	0.491	<0.05
Plasma leptin (pm)	Dopamine	0.583	0.743	<0.01
	irβ-lipotropin	0.417	0.120	NS
	TT3	−0.516	−0.084	NS
	UFC	0.556	0.317	NS

pr, Partial correlations controlling for BMI.
[a] All correlations were significant ($P < 0.05$) before controlling for BMI.

to leptin. Cigarette smoking has previously been reported to predict circulating leptin levels (37). However, this relationship was weak ($P < 0.1$), and so our finding of a lack of any predictive value of smoking use on leptin levels was not surprising. A more reliable predictor of cigarette smoking, at least after an overnight period of abstinence, appears to be decreased CSF levels of the dopamine metabolite HVA (32).

A history of combat-related PTSD, although not significantly associated with changes in leptin concentrations, was found to be associated with elevated levels of irβ-lipotropin (27) and decreased TT_3. However, irβ-lipotropin and TT_3 were also strongly interrelated with levels of body fat, which were higher among the veterans in this particular sample. BMI, in fact, was associated with many of the neuroendocrine variables measured besides irβ-lipotropin and TT_3, including plasma IL-6, UFC, and CSF 5HIAA. Similar findings in healthy volunteers have been found between BMI and IL-6 (38) and cortisol (39). Our findings support the reliability of such interactions and stress the importance of considering body fat levels when interpreting the significance of hormone/neurotransmitter covariability.

Of primary interest are those variables that were found to be associated with leptin levels independently of BMI, namely 24-h UFC excretion and dopamine. The positive relationship between UFC and leptin observed here is consistent with a number of other observations. In humans, oral administration of cortisol has been shown to produce dose- and time-dependent increases in plasma leptin levels (40), and patients with acute sepsis and elevated plasma cortisol concentrations also have 3-fold higher concentrations of plasma leptin relative to healthy controls (41). These elevations, however, may have been due to administration of steady glucose infusions that would disrupt the normal diurnal pattern of circulating leptin concentrations seen with intake of regular meals (4). The mechanism for the relationship between UFC and leptin, however, is also somewhat unclear. UFC levels are a product of activity of the hypothalamic CRH system as part of the classic hypothalamic-

pituitary-adrenal axis. Hence one possible explanation for the relationship between UFC and leptin would be a direct action of leptin to increase CRH activity in the hypothalamus. Several lines of evidence from rodent (22, 42–44) and hypothalamic explant studies (45) do indeed point to leptin increasing CRH activity, although some degree of controversy regarding this topic remains (46, 47). However, the current data show no relationship between CRH and leptin or between CRH and UFC. This suggests two possible hypotheses. First, the relationship between leptin and UFC may not be mediated by the CRH system, but by some other mechanism. Alternatively, the CRH measurements in CSF reported here are the product of predominantly extrahypothalamic sources of CRH (48) and thereby obscure the relationship between leptin and hypothalamic CRH as well as between UFC and hypothalamic CRH.

Of the neurotransmitters assayed in CSF, dopamine was strongly correlated with plasma leptin levels. Both plasma leptin and CSF dopamine were positively correlated independent of adiposity, as assessed be the BMI. Interestingly, in contrast to the vast number of studies devoted to leptin-HPA interactions, virtually none has explored the potential interaction between leptin and dopamine. Similar to the anorectic effect of leptin in animals, pharmacological agents that increase dopamine release or inhibit dopamine reuptake, such as cocaine and amphetamines, are well known to potently reduce appetite in animals and humans (49, 50). Bromocriptine, a dopamine D2 agonist, and other dopamine agonists, including SKF38393 and BC/SKF, alone and in combination dramatically reduce body fat, glucose, and insulin levels in hamsters (51) and *ob/ob* mice (52). These agents also appear to improve basal insulin release in *ob/ob* mice (53) and ameliorate islet dysfunction in *db/db* mice (54).

In obese, nondiabetic, hyperinsulinemic women, bromocriptine significantly decreases cholesterol, PRL, glucose, and tryglyceride levels (55). Taken daily, bromocriptine produces a 25% reduction of body fat after 6 weeks in females and reduces hyperglycemia in diabetic subjects (56). High insulin and glucose levels are associated with increased plasma leptin (37, 57, 58), which may also be regulated by a dopamine system (52). Furthermore, the existence of leptin receptors on tyrosine hydroxylase (dopamine-synthesizing) neurons in the dorsomedial nucleus of the hypothalamus lends neuroanatomical support for a leptin-dopamine interaction (59).

In summary, our data show a consistent covariation in humans between CSF and plasma leptin concentrations that is sustained throughout 18 h of fasting. Fasting was associated with a significant decline in CSF as well as plasma leptin levels. The present data also reveal several relationships between leptin and other neuroendocrine parameters, such as 5HIAA, irβ-lipotropin, TT_3, and IL-6, that were largely dependent on BMI. These observations underscore the importance of assessing the influence of BMI or adipose mass in clinical studies of CNS neuroendocrine parameters. Of particular interest was the positive and independent relationships between CSF leptin levels and 24-h UFC excretion and between plasma leptin levels and CSF dopamine concentrations. These relationships remained strong despite a decline in leptin with continued food restriction. These findings suggest additional roles for leptin in neuroendocrine regulation that may contribute to the central regulation of food intake and energy balance. Furthermore, this study raises the possibility that dopaminergic systems are involved in the effects of leptin, and this interaction might be dysregulated in obesity. It is therefore possible that the mechanism by which dopamine agents ameliorate symptoms of diabetes and obesity involves leptin. Prospective studies of individuals with obesity, diabetes, and other disorders of compromised neuroendocrine and metabolic systems are needed to elucidate the role of leptin interactions with glucocorticoids and dopamine in the etiology and maintenance of these conditions and to help develop efficacious treatment strategies.

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