Leptin response to short-term fasting in sympathectomized men: role of the SNS

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Jeon, Justin Y., Vicki J. Harber, and Robert D. Steadward. Leptin response to short-term fasting in sympathectomized men: role of the SNS. Am J Physiol Endocrinol Metab 284: E634–E640, 2003. First published November 12, 2002; 10.1152/ajpendo.00302.2002.—We studied plasma leptin levels in six people with high-lesion spinal cord injury (SCI; body mass index [BMI] 25.9 ± 1.5 kg/m², age 37 ± 3.0 yr) and six able-bodied (AB) controls (BMI 29.1 ± 1.9 kg/m², age 35 ± 3.5 yr) before and after 12, 24, and 36 h of fasting. The plasma leptin levels significantly decreased during 36 h fasting by 48.8 ± 4.5% (pre: 11.3 ± 2.3, post: 6.2 ± 1.5 ng/ml) and 38.6 ± 7.9% (pre: 7.6 ± 5.0, post: 4.2 ± 1.0 ng/ml) in SCI and AB, respectively. Plasma leptin started to decrease at 24 h of fasting in the SCI group, whereas plasma leptin started to decrease at 12 h of fasting in the AB group. The current study demonstrated that plasma leptin decreased with fasting in both SCI and AB groups, with the leptin decrease being delayed in the SCI group. The delayed leptin response to fasting in the SCI group may be because of increased fat mass (%body fat, SCI: 33.8 ± 3.0, AB: 24.1 ± 2.9) and sympathetic nervous system dysfunction.

spinal cord injury; tetraplegia; ob gene; diabetes; sympathetic nervous system; spinal cord injury

LEPTIN, THE PRODUCT OF THE OBESE GENE, is a 16-kDa protein produced by adipocytes (58) that is delivered to the brain, primarily to the hypothalamus (6, 18). Administration of exogenous leptin to the medial basal hypothalamus in normal mice (2), rats (56), and monkeys (50) effectively decreases food intake and increases energy expenditure. Also, synthesis and secretion of leptin are increased in proportion to the degree of adiposity in several models of rodent obesity (15) and human obesity (4, 9), suggesting that leptin may represent one of the defense mechanisms against the development of obesity (30).

There is increasing evidence that another important function of leptin is to regulate the neuroendocrine response to fasting (1). In lean persons, plasma leptin concentrations decline markedly within the first 24 h of fasting, which may be important in regulating substrate metabolism and energy expenditure during early starvation (5, 17, 55). Weiss et al. (55) reported up to a 66% decline in plasma leptin levels after 1 wk of energy restriction. Decreases in the fasting-induced plasma leptin levels were prevented by maintaining euglycemia via glucose infusion during 72 h of fasting (5). Sonnenberg et al. (48) reported that plasma leptin levels declined steadily and significantly during 26 h of fasting. However, when the plasma leptin levels remained constant through glucose infusion, leptin levels did not change. These studies have provided convincing evidence that leptin has a role as an afferent signal of glucose availability to the central nervous system for modulating both long-term and short-term energy imbalance (1, 17, 54). This function of leptin defends the body from excess energy expenditure in the face of limited energy intake (1, 56).

One of the possible mechanisms of the modulation of leptin secretion during fasting may involve the sympathetic nervous system (SNS; see Ref. 14). Sivitz et al. (47) reported that the administration of α-methyl-p-tyrosine methyl ester (AMPT-ME) increased plasma leptin 15-fold, increased epididymal fat leptin mRNA up to 2.5-fold, increased interscapular brown adipose tissue leptin mRNA, and decreased lumbar sympathetic nerve activity. Rayner et al. (41) also presented complementary findings by showing that administration of AMPT produced hyperleptinemia in mice. Because AMPT-ME inhibits catecholamine production, the increased leptin levels after administration of AMPT-ME most likely suggest that catecholamines are required for normal leptin secretion and lack of sympathetic nerve innervation would increase leptin levels. In addition, epinephrine and norepinephrine infusions acutely decreases ob gene expression and plasma leptin levels (8, 39). It is assumed that a regulatory pathway involving the suppression of leptin release acts through sympathetic activation of adipose adrenergic receptors (41, 43, 47). The data suggest that the SNS may play a key role in the modulation of leptin during fasting.

People with spinal cord injury (SCI) have experienced the dysfunction of the SNS, which results in an altered hormonal and metabolic response during fasting in humans (49, 56). Palmer et al. (38) investigated...
the catecholamine response to insulin-induced hypoglycemia in subjects with high-lesion SCI and in able-bodied (AB) subjects. They found that catecholamine did not increase in people with high-lesion SCI, whereas it increased >200% in AB controls. This result was confirmed by another study (32) that reported a 12.8-fold increase in norepinephrine during insulin-induced hypoglycemia in AB controls while no changes were observed in the high-lesion SCI group. Although the afferent limb of the baroreceptor arc is intact, the lesion in people with high-lesion SCI disrupts the sympathetic component of the efferent limb in the cervical spinal cord. This results in their inability to increase sympathetic nerve activity during fasting (32).

Because intact SNS is required for normal leptin action (7, 8) and catecholamine response to fasting, it is important to determine the leptin response to short-term fasting in people with high-lesion SCI. However, leptin response to fasting has not been investigated in people with SCI whose SNS is impaired. Therefore, the purpose of the study was to determine the leptin response to 0, 12, 24, and 36 h of fasting in the SCI and AB groups.

METHODS

Subjects. Six male subjects with complete SCI (C5–C7, complete lesion) and six male AB subjects participated in the study. Subjects were matched by age, weight, height, body mass index (BMI), and waist circumference, and no participants had type 2 diabetes mellitus or coronary heart disease. Written informed consent was obtained before participation in the study, which was approved by the University of Alberta Ethics Review Board. Subjects were asked to abstain from any strenuous physical activity during the period of study. Subject characteristics are summarized in Table 1.

Experimental procedure. At 1800, subjects consumed a standard meal (55% carbohydrate, 30% fat, and 15% protein) containing 12 kcal/kg body wt for lean subjects and 12 kcal/kg adjusted body wt for obese subjects [BMI >30; adjusted body wt = ideal body wt + (actual body wt - ideal body wt × 0.25)]; see Ref. 31. At 2100, a snack (140 kcal, 27 g carbohydrate, 2.7 g fat, and 8.8 g protein) was ingested by every subject. After the snack, subjects were asked not to consume any food except water until 0900 of day 3. At 0900 and 2100 of day 2 and 0900 of day 3 (12, 24, and 36 h of fasting, respectively), subjects were asked to come to the laboratory, and blood samples (18 ml) were collected in heparinized tubes. Blood samples were centrifuged immediately (4°C), separated, and frozen (−80°C) until an analysis was performed.

Resting metabolic rate. Oxygen consumption at rest was used to calculate the resting metabolic rate (RMR) and fuel utilization. RMR was measured at 0800 of day 2 and day 3. The subjects rested in a supine position for 30 min before measurement. A transparent canopy was placed over the heads of the subjects while oxygen consumption was measured. Subjects were not permitted to sleep or move during the testing. Energy expenditure was calculated using the Weir equation (model CPX-D; MedGraphics, Minneapolis, MN; see Ref. 54).

Body composition. Fat mass, fat-free mass (FFM), abdominal obesity, and percent body fat were determined by a trained technician using dual-energy X-ray absorptiometry (DEXA; Hologic QDR 4500A; Hologic, Waltham, MA) on all subjects according to a previously published procedure (21). With the participant lying supine, and with all metal objects removed, a series of transverse scans was made from head to toe at a standardized transverse scan speed of 5 cm/s. DEXA has been shown to be the most practical and accurate way to measure body composition in people with SCI (21).

Analytical procedures. All samples from each subject were analyzed in one assay to avoid between-assay variation. Plasma leptin levels (ng/ml) were measured in duplicate at each time point by RIA (Human leptin RIA; Linco Research, St. Charles, MO). The limit of sensitivity was 0.5 ng/ml. The intra-assay coefficient of variation (CV) was 4.7%. Plasma insulin levels (µU/ml) were measured in duplicate at each time point by RIA (Human insulin RIA; Linco Research, St. Louis, MO). The intra-assay CV was 7%. Plasma growth hormone (GH) levels (ng/ml) were measured in duplicate at each time point by RIA (Diagnostic Products, Los Angeles, CA). The intra-assay CV was 6.9%. Growth hormone (GH) levels were measured in duplicate at each time point by RIA (Diagnostic Products). The intra-assay CV was 10.5%. Glucose levels were measured by the enzymatic method (Glucose analyzer II; Beckman Instrument, Irvine, CA). Plasma epinephrine (pmol/l) and norepinephrine (nmol/l) levels were measured by HPLC with electrochemical detection (electrochemical detector model 1045; Hewlett-Packard, Waldbronn, Germany; see Ref. 26). The intra-assay CV for these assays was 7% for epinephrine and 9.8% for norepinephrine.

Statistical analysis. The statistical analysis was performed by a two-way ANOVA repeated measurement; between-groups (SCI vs. AB) and within-subject (0, 12, 24, and 36 h of fasting) factors and their interaction were considered. Comparisons among the variables between the two groups were made by independent t-tests. Pearson’s product-moment correlation was used to measure the strength of association between the variables. Stepwise multiple linear regression was used to determine the strongest predictor for RMR (dependent variable) among leptin, FFM, and GH (independent variables). All data have been expressed as means ± SE. Statistical significance was set for P < 0.05.

RESULTS

Plasma leptin response to fasting. At 0 h of fasting, plasma leptin was higher in the SCI group compared

Table 1. Characteristics of subjects

<table>
<thead>
<tr>
<th>Value</th>
<th>SCI (n = 6)</th>
<th>AB (n = 6)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>37.0 ± 3.0</td>
<td>35 ± 3.5</td>
<td>0.47</td>
</tr>
<tr>
<td>Height, cm</td>
<td>175.8 ± 2.9</td>
<td>176.6 ± 1.4</td>
<td>0.80</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.6 ± 6.0</td>
<td>90.7 ± 5.0</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9 ± 1.5</td>
<td>29.1 ± 1.9</td>
<td>0.22</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>33.8 ± 3.0</td>
<td>24.1 ± 2.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>27.1 ± 3.7</td>
<td>21.6 ± 3.3</td>
<td>0.30</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>49.4 ± 2.3</td>
<td>63.2 ± 1.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>12.0 ± 2.6</td>
<td>6.1 ± 1.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>89.0 ± 4.7</td>
<td>92.9 ± 3.0</td>
<td>0.58</td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
<td>12.8 ± 4.4</td>
<td>12.2 ± 2.9</td>
<td>0.97</td>
</tr>
<tr>
<td>GH, ng/ml</td>
<td>0.4 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Epi, pmol/l</td>
<td>19.0 ± 1.0</td>
<td>124.5 ± 27.4</td>
<td>0.01</td>
</tr>
<tr>
<td>NE, nmol/l</td>
<td>0.5 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RMR, kcal/day</td>
<td>1,489 ± 89</td>
<td>1,812 ± 70.5</td>
<td>0.04</td>
</tr>
<tr>
<td>RMR/FFM, kcal/day⁻¹·kg⁻¹</td>
<td>30.3 ± 1.6</td>
<td>28.7 ± 1.6</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Data are means ± SE; n, no. of subjects. SCI, spinal cord injury; AB, able bodied; BMI, body mass index; FFM, fat-free mass; Epi, epinephrine; NE, norepinephrine; GH, growth hormone; RMR, resting metabolic rate.
with the AB group; however, the difference did not reach statistical significance. During the 36-h fasting period, plasma leptin decreased significantly below the prefasting level in both the SCI (0 h fasting: 11.34 ± 2.27 vs. 36 h fasting: 6.16 ± 1.46 ng/ml) and the AB (0 h: 7.58 ± 2.05 vs. 36 h: 4.18 ± 1.01 ng/ml) groups. Plasma leptin started to decrease at 24 h and continued to decrease until 36 h of fasting in the SCI group, whereas it started to decrease at 12 h and started to plateau after 24 h of fasting in the AB group (Fig. 1). When the BMI was controlled, the two-way ANOVA repeated measurement showed an interaction between leptin responses to fasting in the groups (P = 0.011).

**Plasma hormone and metabolite response to fasting.** There was no significant difference in plasma glucose, insulin, cortisol, and GH before fasting between the groups. There was no significant difference in the hormones and the glucose response during 36 h of fasting in either group.

**RMR.** Absolute RMR (kcal/day) was higher in the AB vs. SCI group at both 12 and 36 h of fasting. However, there were no differences between the groups in relative RMR (kcal·day⁻¹·kg FFM⁻¹) at either 12 or 36 h of fasting. Over the 36-h period of fasting, RMR (absolute and relative) values did not change in either group.

**Relationship between RMR and plasma leptin during fasting.** Positive correlations were found between leptin levels and RMR (absolute and relative) in the AB group. On the other hand, no correlations were found between leptin levels and RMR (absolute and relative) in the SCI group at either 12 or 36 h of fasting (Fig. 2).

**Body composition.** Although subjects were matched for age, weight, height, BMI, and waist circumference, the SCI group showed a significantly higher percentage of body fat (33.8 ± 3.0 vs. 24.4 ± 2.5%), resulting from higher fat mass (27.1 ± 3.7 vs. 21.6 ± 3.3) and lower FFM (49.4 ± 2.3 vs. 63.41 ± 2.96), compared with the AB group (Table 2).

**DISCUSSION**

To our knowledge, the present study was the first to examine the leptin response to a 36-h fast in SCI and AB individuals. We demonstrated that leptin levels declined in both groups but was delayed in the SCI volunteers.

**Leptin response to short-term fasting.** A fasting-induced decrease in plasma leptin plays an important role in initiating changes in substrate metabolism and energy expenditure (44, 50). In humans, a significant reduction of energy intake or fasting suppresses leptin levels to a much greater extent than would be expected on the basis of changes in the adipose tissue mass (5, 17, 24). This is consistent with evidence that leptin has a role as a signal of energy deficiency and an integrator of neuroendocrine function (1). The present study demonstrated that plasma leptin decreased with 36 h of fasting by 48.8 ± 4.5 and 38.6 ± 7.9% in both the SCI and the AB groups, respectively. The literature in this area suggests that short-term fasting (12 h) reduces plasma leptin levels in the AB population (5, 29). Our
epinephrine stimulates adipose tissue restriction (19, 20, 25, 24). Fasting-induced secretion of leptin in individuals has a blunted leptin response to food in-take, which also reduces whole body lipolytic sensitivity, and obese individuals show a delayed leptin response to fasting. Excessive adiposity is known to re-duce the SNS system. Hence, removal of this inhibition, as a result of fasting in SCI, may be because of an impairment in SCI. Therefore, the delayed leptin response during fasting in the SCI group may be because of an impairment of the SNS system.

In addition to SNS dysfunction, the significantly higher percentage of body fat in our SCI group may be another factor contributing to the delayed leptin response to fasting. Excessive adiposity is known to reduce whole body lipolytic sensitivity, and obese individuals have a blunted leptin response to food restriction (19, 20, 25, 24). Fasting-induced secretion of epinephrine stimulates adipose tissue β-adrenergic receptors and leads to increased lipolysis and decreased leptin concentrations (19, 20, 24). The failure of circulating levels of epinephrine to increase in our SCI subjects is likely because of their SNS dysfunction. Furthermore, their higher levels of body fat could further reduce lipolytic sensitivity (19, 20, 25). These results suggest that the delayed leptin decline during fasting in the SCI group may be because of both SNS dysfunction and decreased lipolytic sensitivity accompanied by increased fat mass.

Mechanisms for fasting-induced leptin decline. Both the SCI and AB groups experienced a significant decrease in plasma leptin levels, although the SCI group showed a delayed leptin response to fasting, which may suggest that adrenergic mechanisms are not the sole mechanism of leptin production and/or regulation during fasting. For example, evidence suggests that glucose metabolism is partly responsible for leptin production in humans (5, 17). The importance of glucose metabolism in regulating the level of leptin was demonstrated by Boden et al. (5), who found that glucose infusion during fasting prevented the fast-induced leptin decline. Also, Sonnenberg et al. (48) reported that plasma leptin levels declined steadily and significantly during 26 h of fasting. When the plasma glucose levels remained constant between 104 and 117 mg/dl via glucose infusion, the leptin level did not change during fasting. The plasma leptin even increased during 26 h of fasting when glucose levels were increased >157 mg/dl via glucose infusion. These studies have provided convincing evidence that the plasma glucose level is one of the major contributors for leptin production. Wang et al. (53) suggested that glucoregulation of leptin production may be mediated by the entry of glucose in the glucosamine pathway via L-glutamine, the D-fructose-6-phosphate amidotransferase step.

Another leptin-regulatory factor during fasting may be circulating insulin. Barr et al. (3) showed that treatment of rat adipocytes with insulin increased tissue leptin content and secretion during a 2-h incubation period. Also, insulin administration increased leptin release within 10 min, suggesting that insulin may act as a leptin secretagogue (27). Other studies have demonstrated that leptin administration inhibited insulin secretion (35). Our findings would support the hypothesis of an SNS-mediated leptin-insulin interaction. There was a positive correlation between the 36-h fasting leptin levels and the 36-h fasting insulin levels in the AB group (r = 0.83, P = 0.04), but no similar correlation was identified in the SCI group (r = 0.61, P = 0.20).

Relationship between plasma leptin and RMR. The present study showed that plasma leptin positively correlated with RMR (absolute and relative) in the AB group. When a multiple stepwise forward regression analysis was performed with the RMR as the dependent variable and with the plasma leptin, FFM, and GH as the independent variables, plasma leptin was the strongest predictor of RMR, accounting for 74.5% of the RMR variation. Together with the previous demonstration that the leptin level is a positive determinant of RMR in men, Pima children, women with anorexia nervosa, and patients with heart failure (22, 31, 40, 42, 51), the present study supports the hypothesis that leptin is a significant factor in the regulation of energy expenditure in humans. In contrast, leptin was not correlated with RMR (absolute and relative) in the SCI group. This result supports the hypothesis that normal SNS function is required for leptin to influence energy expenditure. Administration of exogenous leptin or activation of the gene that encodes for leptin in

Table 2. RMR

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>RMR, kcal/day</td>
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has resulted in increased energy expenditure, increased glucose uptake, and decreased insulin secretion. The enhanced rate of glucose uptake and decreased insulin secretion resulting from administration of leptin was suppressed effectively with surgical sympathetic denervation of the tissue (18, 33–35). Also, increased glucose uptake in skeletal and heart muscles was prevented completely by pretreatment with guanethidine but not by adrenal demedullation (18). Because guanethidine does not inhibit secretion of epinephrine from the adrenal medulla and does not affect brain norepinephrine, these results suggest that the SNS mediates the effects of leptin.

Monroe et al. (36) examined the effects of intravenous propranolol infusion, a β-adrenergic blocker, on RMR. They demonstrated that β-adrenergic blockade acutely decreased RMR, suggesting that a tonic SNS β-adrenergic effect in healthy adult humans was operating. The literature also suggested that the activity of the SNS was a determinant of energy expenditure and that individuals with low resting SNS may be at risk for body weight gain because of the lower metabolic rate (45). Therefore, it is likely that leptin increases overall sympathetic nerve activity, thereby leading to a significant increase in energy expenditure. It follows that the decentralization of the SNS may interrupt the pathway of leptin-mediated energy expenditure regulation in this study. Therefore, the lack of association between leptin and RMR in the SCI group in this study may be because of the dysfunction of the SNS.

The effect of short-term fasting on RMR is controversial (57). Hypoglycemia is known to increase the level of SNS activity and increase the release of norepinephrine (38), which in turn causes an increased rate of lipolysis to compensate for the decreased level of glucose (20, 24). The increased level of norepinephrine resulting from hypoglycemia would also increase energy expenditure (36). However, it has also been demonstrated that hypoglycemia decreases circulating leptin levels in animal and human models (5, 24), which would result in decreased SNS activity. Because norepinephrine is a marker of the level of SNS activity, decreased SNS activity would theoretically decrease energy expenditure (37). Thus the response of SNS to fasting is paradoxical and requires further investigation and explanation. Our study suggests that RMR does not change with 36 h of fasting in either the AB or SCI group compared with the level obtained from 12 h of fasting in both SCI and AB groups. However, Zauner et al. (57) reported that RMR in short-term fasting is increased as a result of an increase in serum norepinephrine. They measured resting energy expenditure after 36, 60, and 84 h of fasting and found that norepinephrine concentration increased from 1,716 ± 574 to 3,728 ± 1,636 pmol/l. The resting energy expenditure was increased from 3.97 ± 0.9 kJ/min at 12 h of fasting to 4.53 ± 0.9 kJ/min at 84 h of fasting.

In conclusion, the leptin decline in response to short-term fasting is delayed in the SCI group. The altered response in leptin secretion in the SCI group with short-term fasting may be because of SNS dysfunction and increased adiposity. However, other mechanisms may influence leptin production during fasting (i.e., glucose and insulin levels). Leptin was a strong determinant of energy expenditure in the AB group, which suggests that leptin-mediated regulation of energy expenditure requires an intact SNS.

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REFERENCES


