REPORTS OF A RELATIONSHIP between altitude and circulating levels of leptin suggest a possible role of hypoxia in leptin regulation. However, studies on the changes in plasma leptin levels at altitude are controversial, with some showing an increase and others suggesting no change or a fall in these levels. Exposure to hypoxia has been shown to stimulate hypoxia-inducible factor 1 (HIF-1), which appears to be an important regulator for the expression of the leptin gene. However, there are a number of other variables that may influence the altitude-leptin relationship that could explain these divergent findings, such as cold exposure, physical activity, and diet, among others. Some of the studies presented suggest that hypoxia directly stimulates leptin release under controlled experimental conditions, whereas leptin levels may paradoxically decrease in response to certain physiological conditions associated with altitude. In conclusion, all confounding factors associated with altitude should be considered when assessing the leptin-altitude relationship.

Introduction. Leptin is a protein (~16 kDa in mass) hormone produced by adipose tissue with regulatory effects on metabolism and body weight. It is encoded by the obese (ob) gene and circulates to the brain and interacts with receptors in the hypothalamus to inhibit eating (14, 15). Recently, there has been some controversy regarding the role of leptin in high-altitude studies. Basically, there are two opposite positions. The first supports that leptin levels increase with exposure to high altitude (4, 9, 15, 17) and the second supports that leptin levels decrease with exposure to high altitude (2, 16, 20).

Given the altitude effects on circulating levels of leptin and the controversy created by the effect of high altitude on leptin, we would like to demonstrate the link between hypoxia and leptin and suggest a possible explanation for the ongoing controversy.

Evidence of increased or unchanged leptin levels with altitude. In a prospective study of 20 healthy males, Tschop and colleagues (15) reported elevated plasma leptin levels in human subjects at high altitude, leading to loss of appetite, increased energy expenditure, and weight loss. In a recent study, Shukla and colleagues (11) reported elevated plasma levels of leptin and weight loss after exposure to hypoxic conditions for 7 days in a group of 30 lowlanders who had never visited high altitudes before. In a cross-sectional study of 55 healthy men, Woolcott and colleagues (17) reported no statistical difference between plasma leptin levels in three different populations of dwellers from sea level and two places in the Peruvian Andes. In an intervention study, Barnholt and colleagues (1) reported that leptin concentrations did not change after exposure to hypoxia regardless of energy intake. Other studies have suggested elevations in leptin levels in patient populations that may be associated with chronic hypoxia or intermittent hypoxia, such as sleep apnea (4, 9; see Table 1).

Evidence of decreased leptin levels with altitude. In a prospective study of 10 healthy males, Vats and colleagues (16) reported that leptin levels decrease significantly after 7 days of acute exposure to high altitudes (3,600 and 4,580 m) compared with their baseline leptin measurements at sea level. Recently, in a prospective study of 12 healthy males, Zaccaria and colleagues reported that subjects exposed 15–20 days to high altitude (5,050 m) decreased their plasma leptin levels compared with their baseline leptin measurements at sea level (20). Also recently, Cabrera de Leon and colleagues (2) reported that serum leptin levels decrease when altitude increases in a cross-sectional cohort of 889 subjects in the Canary Islands, Spain, at a relatively low altitude (200–1,020 m; Ref. 2).

Hypothesis. On the basis of these observations, we therefore hypothesize that altitude stimulates leptin release through hypoxia-sensitive mechanisms. However, there are many factors that can alter this relationship.

Mechanistic considerations. Regarding the evidence that altitude increases levels of leptin, there is one hypothesis that might explain this. HIF-1 is a transcription factor of major importance in the cellular response to oxygen deficiency such as the one experienced at high altitude. It is important that this critical transcription factor be tightly regulated for cells to respond to a wide range of oxygen concentrations. Exposure to hypoxia has been shown to stimulate HIF-1, which appears to be an important regulator for the expression of the leptin gene (4). Furthermore, hypoxia appears to upregulate leptin expression depending on the degree of obesity, as a recent animal study reported that despite no different hematologic responses to hypoxia in lean and obese rats, activation of two hypoxia target genes in the adipose tissue was only seen in the obese. Showing perhaps a hypoxic sensitivity genotype in the obese produced by hypertrophy of the adipose tissue perhaps it is a counterregulation in the lean that impedes leptin gene stimulation (13, 19).

The results of the two cross-sectional studies (1, 17) that did not report changes in leptin levels could be due to the fact that these subjects were genetically adapted to live at high altitudes. Furthermore, recent animal studies have shown that hypoxia in adipose tissues underlies the dysregulated production of adipocytokines and metabolic syndrome in obesity (6, 18). Hence, leptin expression induced by hypoxia appears to be heavily influenced by genetic and obesity factors.

As for the evidence that circulating leptin decreases with altitude, there are many confounders that have not been adequately addressed in the negative studies presented, which may...
Table 1. Summary of studies reporting leptin concentrations after hypoxia exposure

<table>
<thead>
<tr>
<th>First Author/Year</th>
<th>Leptin</th>
<th>Degree of Hypoxia</th>
<th>Duration of Exposure/n</th>
<th>Weight Change</th>
<th>Age</th>
<th>Possible Confounding Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tschop (15)/1998</td>
<td>Increase</td>
<td>4,559 mts</td>
<td>1–2 days/20</td>
<td>Weight loss</td>
<td>19–42</td>
<td>Cold exposure, physical activity</td>
</tr>
<tr>
<td>Shukla (11)/2005</td>
<td>Increase</td>
<td>3,600–4,550 mts</td>
<td>7 days/30</td>
<td>Weight loss</td>
<td>20–25</td>
<td>Not reported</td>
</tr>
<tr>
<td>Woolcott (17)/2002</td>
<td>No change</td>
<td>3,250–4,550 mts</td>
<td>Chronic, cross sectional/55</td>
<td>Not reported</td>
<td>20–30</td>
<td>Cold exposure, physical activity, diet</td>
</tr>
<tr>
<td>Barnholt (1)/2006</td>
<td>No change</td>
<td>4,300 mts</td>
<td>21 days/26</td>
<td>Weight loss</td>
<td>18–35</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cabrera de Leon (2)/2004</td>
<td>Decrease</td>
<td>200–1,200 mts</td>
<td>Chronic, Cross sectional study/889</td>
<td>Weight loss</td>
<td>19–29</td>
<td>Cold exposure, physical activity, diet</td>
</tr>
<tr>
<td>Vats (16)/2004</td>
<td>Decrease</td>
<td>3,600–4,580 mts</td>
<td>7 days</td>
<td>Weight loss</td>
<td>26–47</td>
<td>Cold exposure, physical activity, diet</td>
</tr>
<tr>
<td>Zaccaria (20)/2004</td>
<td>Decrease</td>
<td>5,050 mts</td>
<td>15–20 days/12</td>
<td>Weight loss</td>
<td>13–70</td>
<td>Genetically adapted</td>
</tr>
</tbody>
</table>

alter the altitude-leptin relationship (12). Cold exposure and weight loss have been related with decreased leptin production, creating a “starvation signal” to the body. This might help explain why in acute exposure to hypoxia and extreme cold, the levels of leptin are diminished. Subjects in these studies were exposed to both hypobaric hypoxia and the cold environment of high altitude, and the changes seen in leptin levels might be a combined effect of hypoxia and cold. Other factors that can affect leptin levels are physical activity and diet. Many of the studies that reported decreased leptin levels failed to adequately control for these and other factors. Also, the inhalation of carbon monoxide (CO) can have a negative effect on leptin gene expression and translation, and reduced levels of leptin have been reported in smokers (7). Hypoxia also leads to an increase in neural sympathetic activity, in particular catecholamines, which in turn inhibit leptin gene expression through the β-adrenergic receptors (3). It is interesting to note that in obese rats, the response of fat cells to catecholamines is impaired (8). Finally, circulating leptin levels show diurnal variation with a particular nocturnal rise increasing in the morning (10).

All these potential confounders alone or in combination could clearly alter the effects that hypoxia may have on leptin expression. Exposure to altitude is usually accompanied by increased activity levels, weight loss, altered hydration, cold exposure, sympathetic activation, and altered sleep patterns, all of which are potential modulators of leptin.

Conclusion. Some of the studies presented suggest that hypoxia directly stimulates leptin release under controlled experimental conditions, whereas leptin levels may paradoxically decrease in response to certain physiological conditions associated with altitude. Therefore, all confounding factors associated with altitude should be considered when assessing the leptin-altitude relationship.

REFERENCES


