THINNER IN THIN AIR: IS WEIGHT LOSS AT HIGH ALTITUDE HORMONALLY MEDIATED?

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Introduction

Loss of weight and appetite occur frequently at altitudes above 5000 m, but little is known of the pathophysiology of weight loss and changes in body composition at extreme altitude. Weight loss at high altitude appears to result from a marked difference between energy intake and energy expenditure. Proper acclimatisation to altitude and high caloric intake with a wide variety of nutrients can help to minimise but cannot completely prevent significant weight loss at high altitude (1). The effect high altitude has on metabolic systems related to weight maintenance is not fully understood. The effects of altitude are being reexamined in light of new information into the physiological controls of weight. This article will briefly review what is known about weight loss at high altitude, and will examine further newer information on the endocrinology of energy homeostasis, and the effects of high altitude exposure on this balance.

Weight loss at high altitude

Numerous studies have sought to further clarify the anthropometric changes that occur at high altitude, and the reasons for them. The degree of weight loss varies depending on altitude achieved, and length of stay there, and has been as extreme as 8.9% of body weight at outset after a 62 day expedition to 8047m (2). In most studies, the majority of the weight loss is attributable to fat loss (3, 4, 5, 6, 14, 7, 9) although decreases in muscle mass, accompanied by a negative nitrogen balance also occur (4, 10). One study has suggested however, that although under 5000 m 70% of the weight loss is fat loss, over 5000m only 27.4% of weight loss is secondary to loss of fat (3). Effects were not consistent over all groups, as Sherpas who showed half as much body fat as the mountaineers, maintained their weight during residence above 5,400m.

Decreased caloric intake (4, 12) and a negative energy balance (7, 8) have been noted at high altitude, and these were considered the major contributors to weight loss (11). However, efforts to overcome this with a wider variation in food stuffs does not fully prevent weight loss (6). Malabsorption of fat has also been noted, but is not confirmed in all studies (13, 14).

An interesting study, to determine whether hypoxia due to decompression causes weight loss was conducted by the US Army Research Institute of Environmental Medicine. Six men, provided with a palatable ad libitum diet, were studied during progressive decompression to 240 Torr over 40 days in a hypobaric chamber where hypoxia was the major environmental variable. Caloric intake decreased 43.0% from 3,136 to 1,789 kcal/day ($p<0.001$). Over the 40 days of the study the subjects lost 7.4±2.2 (SD) kg and 1.6% (2.5 kg) of the total body weight as fat. Computerized

tomographic scans indicated that most of the weight loss was derived from fat-free weight. This study concluded that hypoxia can be sufficient cause for the weight loss and decreased food consumption reported by mountain expeditions at high altitude (10).

Efforts to eliminate weight loss at high altitude have included increasing energy intake, as described above. Researchers have also attempted to ameliorate the effects of altitude with acetazolamide (Az). Bradwell et al., in a placebo-controlled trial, examined exercise performance and muscle mass in 21 acclimatised subjects at an altitude of 4846m. Although weight loss was less and exercise performance was better in the Az treated group (n=11), altitude effects were not completely prevented (15).

It appears, therefore, that hypoxia during high mountain expeditions induces weight loss by hypophagia, and possibly malabsorption and increased metabolic rate.

Weight loss and hormonal changes at high altitude
The factors mediating these changes are not clearly understood. Hundreds of clinical and experimental studies have shown various changes in endocrine parameters at high altitude.

Because of their effect on energy homeostasis, thyroid hormones have been considered a possible contributor to weight loss. At high altitude TSH secretion from the pituitary gland appeared to be enhanced, and total and free thyroxine were found to be elevated, but peripheral conversion from T4 to the active form of thyroid hormone, T3 was impaired. Correlation of these changes with marked weight loss was not found (16), leaving their importance in the weight loss phenomenon in question.

Another important system for the regulation of body composition is the somatotropic axis including growth hormone (GH), growth-hormone-releasing hormone (GHRH), insulin-like growth factor-I (IGF-I) and IGF-binding proteins. Increased hGH response to administration of the GH releasing stimulant GHRH, in healthy volunteers at high altitude has been demonstrated (17), but levels of the effector protein IGF-I remained unchanged. An increase in several IGF-binding proteins (IGFBP-1, 2, 3, 4, 5) at altitude has also been recently reported, but the relation of these to weight loss remains unclear (18).

The first work examining the role of the gonadotropic axis, including LH, FSH, estrogens and androgens, in weight loss at high altitude was published by Martin de Miranda and coworkers in 1977. They showed that weight loss in castrated rats at simulated altitude of 6000 m is not reversible by administration of testosterone or estradiol (19). In most of the studies analysing the function of the gonadotropic axis during hypoxia, no significant changes in LH, FSH, testosterone or estradiol-levels with hypoxia were found compared to normoxic conditions in men (20).

Studies on the effects of hypoxic conditions at high altitude on the CRH-ACTH-Cortisol axis have demonstrated increases in serum cortisol levels with a concomitant loss of the typical diurnal rhythm of ACTH and Cortisol secretion (21).

This increase seems to be suppressible by administration of exogenous corticosteroids (22), and it's relationship to weight changes is unknown.

Changes in endocrine function at high altitude are described frequently, but results and conclusions are often quite contradictory. An endocrine link between the changes induced by hypoxia, and energy homeostasis or weight loss is still missing.

It is not possible to conclude from the literature to date, that a hypoxia induced impairment of the traditional endocrine system (the hypothalamic-pituitary-peripheral glands -axes) can explain the phenomenon of weight loss at high altitude.

Leptin and Energy Homeostasis

Under physiological conditions, weight remains relatively stable, indicating that energy balance may be controlled by a feedback loop, which maintains constancy of total body energy stores. It has been proposed that signals reflecting nutritional state are sensed by the hypothalamus, which, in turn, modulates food intake and energy expenditure. The demonstration that hypothalamic lesions cause hyperphagia, decreased energy expenditure, and obesity have led to the homeostatic models of body weight regulation. Until recently, the key players in this system had not been identified. The discovery of leptin, and other neuropeptides has shed considerable light on what was once a black box.

The leptin story begins with the ob/ob mouse, a mouse strain discovered in the Jackson Laboratories. A recessive gene mutation in the ob/ob mouse produces a phenotype characterised by the behavioural trait of hyperphagia and the morphological trait of obesity, resulting in sterile adult mice with 50% body fat content. Similar phenotypic features are seen in db/db mice, but they also suffer from diabetes. Coleman, from the Jackson Laboratories (23) conducted the famous parabiosis (interindividual cross-circulation) studies in which the ob/ob mice, once exposed to the circulation from db/db mice decreased their food intake and body weight. In contrast, their db/db pairmates, although exposed to the circulation of ob/ob mice, continued to increase their food intake and weight. Coleman concluded, that ob/ob mice fail to produce a circulating factor important in appetite control, that their brains can respond to, whereas db/db-mice make the circulating factor in abundance, but their brains are unable to respond to it. After extensive genetic studies in ob/ob mice, Zhang et al reported in 1994 that they had identified the gene responsible for obesity in these mice, and it encoded a 146 amino-acid protein (plus a 21 amino acid secretory signal sequence). This protein was initially called the obese gene product (24). Because the ob-protein caused a reduction in food intake (as well as an increase in metabolic energy expenditure) it has subsequently been called leptin from the Greek "leptos" for "thin". It is now known that leptin is secreted by adipocytes and, in lesser amounts, also by the placenta and stomach. The finding that intrathecal or peripheral administration of recombinant leptin to diet-induced-obese mice led to impressive weight loss initiated a "leptinomania" in biomedical research, and in the media. In addition to it's role in energy homeostasis, leptin also signals nutritional status to several other physiological systems and modulates their function. This broader role includes effects, at least in rodent models, on pubertal development, fertility, hematopoesis, immune function and angiogenesis.

The initial hypothesis that human obesity is also explained by leptin deficiency has been proven wrong. In general, obese individuals have higher leptin levels, and leptin levels correlate closely with body mass and body fat mass indices. This is not to suggest that leptin deficiency never results in obesity in man. In fact, O´Rahilly et al in 1997 described two young cousins with a genetic leptin deficiency, marked hyperphagia and extreme obesity. Although a rare cause of obesity, these patients have confirmed the essential role of leptin regulation of energy homeostasis in humans (25). The etiology of obesity in the majority of individuals is likely secondary to environmental features leading to a positive energy balance in conjunction with a biological disposition that favours weight gain but defends against weight loss. This picture is consistent with the concept of leptin resistance as opposed to deficiency.

The effects of leptin in reducing food intake, and increasing metabolic energy expenditure are likely to be the basis for drug development aimed at the treatment of obesity in the coming years. (26, 27, 28, 29, 30, 31, 32)

Leptin - a player at high altitude?
As loss of appetite is one of the most frequent symptoms of acute mountain sickness (AMS) (33), as weight loss occurs frequently above 5000 m and, as leptin is a key mediator in the neuroendocrine regulation of energy homeostasis and appetite (35), we investigated the effect of hypobaric hypoxia at high altitude on serum leptin levels in men, using a highly sensitive and specific method for leptin quantification (34, 36). This research was done in collaboration with P. Bärtsch (Heidelberg) and J. Biollaz (Lausanne). We measured mean serum leptin levels in 20 male mountaineers (age: 19-42 years, Capanna Margherita, Switzerland) after active ascent to 4559 m and documented changes in appetite with the Environment Symptom Questionnaire (37). The leptin concentration increased from 1.22±0.19 ng/ml (9:00 a.m. at 120 m, all values mean±SEM) to 2.06±0.34 ng/ml (9:00 a.m at 4559 m, 22 hours after ascent p=0.0003). The mean pO2 at altitude was 43.2 mmHg. This effect on leptin was not reversible after 1 hour of treatment with 33% oxygen-enriched air and appeared to be more pronounced in subjects with loss of appetite (78% increase, n=11), than in those without loss of appetite (52% increase, n=9).

However, physical strain during the active ascent and single measurements of leptin, which is secreted in a pulsatile manner by adipocytes (ca. 32 peaks/24 hours), may have been confounding factors in this study. Therefore, in a second study, serum leptin levels were measured in 18 volunteers (age: 20-41 years) at 490 m (after 1, 4, 12 and 20 hours) and at 4559 m (1, 4, 12, 20 and 32 hours after transportation to 4559 m by helicopter). Appetite was assessed as above, and the diagnosis of Acute Mountain Sickness (AMS) was defined as a functional Lake Louise Score > 1 (5). Twelve of the 18 individuals studied developed loss of appetite, and 10 developed AMS. In individuals with loss of appetite, mean serum leptin levels increased from 3.19±0.89 ng/ml (6°° a.m.at 490 m) to 4.89± 1.18 ng/ml (6°° a.m. at 4559 m, p=0.02), but no significant increase was found in individuals without loss of appetite (2.17 ng/ml vs. 2.55 ng/ml, p=0.35). An increase in integrated serum leptin levels (mean area under the curve) from 53.8±13.8 ng/ml*h to 66.3±16.2 ng/ml*h was also found in individuals with loss of appetite (1-20 hours, p=0.008), but not in those

without loss of appetite (38.7±6.4 ng/ml*h (490 m) vs. 40.8±13.2 ng/ml*h (4559 m), p=0.35).

The 10 individuals who developed AMS, also had a significant increase in their leptin level at 4559m compared to at 490 m (p=0.028). Effects due to change in plasma volume have been excluded. Individuals with loss of appetite tended to have higher leptin levels at baseline than those without loss of appetite (p=0.1), but mean body mass indices were not significantly different between the analysed subgroups. Non-parametric testing (Mann-Whitney test and Wilcoxon test) were used for the statistical analysis.

In summary, in two independent studies, leptin levels increased at high altitude and this increase was found to be associated with loss of appetite. Thus, leptin may be a player in the altered neuroendocrine regulation of energy homeostasis at high altitude, leading to loss of appetite, increased energy expenditure and weight loss. A further link between hypoxia and increased leptin secretion has recently been shown by Mise and coworkers (38). They demonstrated that leptin is also a placentally derived hormone in humans and suggested its significance in human pregnancy. They demonstrated that serum leptin levels were higher in women with pre-eclampsia (PE), a condition associated with placental hypoxia, than in gestational age- and body mass index-matched pregnant women ($p<0.0001$), and the extent of the increase in leptin was associated with disease severity. After delivery, leptin levels returned to those expected for their body mass indices. In addition, leptin mRNA levels were higher in placentas from women with PE than in those from normal women. In vitro studies confirmed that cells cultured under hypoxic conditions had higher leptin levels than those cultured under standard conditions ($p < 0.01$) (38).

Our findings showing increases in leptin at high altitude in individuals with loss of appetite and AMS, in conjunction with the finding that hypoxia alone can trigger anorexia and weight loss, and that leptin levels increase under hypoxic conditions in another biological system, are all consistent with the hypothesis that the hypoxia which occurs at altitude results in an increase in leptin. This increase may result in loss of appetite, anorexia and increases in metabolic rate leading to weight loss.

More players in the endocrine regulation of energy homeostasis

It seems unlikely, however, that leptin alone causes these changes. Under certain conditions various cytokines, for example, are also able to induce anorexia (Plata-Salaman, 1998). We have shown significant increases in circulating interleukin-6, interleukin-1-receptor-antagonist and C-reactive protein in 10 healthy individuals after 2 days at 4559 m. Increased cytokines were also demonstrated in a study of 12 male subjects at an altitude of 3458 m (Jungfraujoch, Switzerland) and were associated with clinical symptoms (39, 40).

Furthermore, there is some evidence that leptin interacts with neuropeptide-Y (NPY), one of the brains most potent neurochemicals involved in appetite. Leptin, NPY and other agents (Melanocorticotropic hormone (MCH), Galanin, Orexin A and B, Peptid YY, Noradrenaline, "Cocaine and amphetamine regulated transcript peptide" (CART), Cholecystokinin, Corticotropin releasing hormone, a-Melanocyte

Stimulating Hormone, Insulin, Phospholipase-1, Bombesin, Urocortin, Serotonin) are involved in a peripheral central circuit which links an adipose tissue signal with central appetite mechanisms and metabolic activity. Within the interaction between excitatory and inhibitory processes there is ample room for the operation of a large number of mediating orexic or anorexic neuromodulating substances (41). There exists an expanding family of hypothalamic modulators of food intake, which includes NPY, and it is likely that leptin modulates the activity of some or all of these factors and that they modulate leptin activity in return. A detailed understanding of the functional relationships between leptin and other neuropeptides and neurotransmitters is necessary to clearly delineate the mechanisms regulating food intake and body weight.

The mystery of weight loss at high altitude has not been solved. However, recent research has begun to reveal new roles for endocrinological investigation in high altitude research. Further studies leading to a more complete understanding of the neuroendocrine regulation of body homeostasis are necessary. Once the triggers for weight loss have been identified and characterised, therapeutic agents that can prevent uncontrollable weight loss in mountaineers during high altitude expeditions are conceivable.

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