Commentaries on Viewpoint: Effect of altitude on leptin levels, does it go up or down?

CONTROL OF LEPTIN WITH ALTITUDE EXPOSURE

TO THE EDITOR: The Viewpoint by Sierra-Johnson et al. (6) raises a number of interesting points about the control of leptin release in response to altitude exposure.

The authors correctly point out that “altitude” can comprise many stimuli to the endocrine system including hypoxia, cold exposure, anorexia, and exercise. In fact, it is likely that these factors interact to make assignment of a mechanism difficult. If one is truly interested in hypoxia per se, simulated altitude can be studied. Although one must always take into account species differences, we found a decrease in leptin in juvenile rats during exposure to normobaric hypoxia for 7 days (5). One of the studies cited by the authors as exposure to high altitude was actually in patients with obstructive sleep apnea at sea level (4). Another study cited as exposure to altitude was actually an in vitro study in which oxygen levels were not manipulated (3). Probably the best study cited did not find an increase in leptin with exposure to hypoxia, although leptin was higher when caloric intake was maintained (1).

Finally, it is a huge leap of faith to assume that hypoxia-inducible factors, which clearly are important in responses to low oxygen in vitro, have anything to do with specific organ responses to tolerable hypoxic exposures in vivo (2).

I can only conclude from the literature in the journal that the jury is still out on the effect of altitude on leptin.

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TO THE EDITOR: Many investigators have shown that leptin levels are in a complex dynamic flux even without hypoxic exposure. Leptin levels change with a circadian rhythm; they are modulated by insulin (1, 5), cortisol (3), hypoxia (2), carbon monoxide, and melatonin (1); and have been associated with food intake, energy expenditure, and whole body energy balance (3). Leptin modulation of the endothelin system is important in pulmonary physiology. The fact leptin plays a regulatory role in immunity, inflammation, hematopoiesis (4), and proangiogenic activity (2) and that HIF-1α protein levels are reduced in wounds of leptin receptor-deficient diabetic mice, underscores leptin level regulation in the presence of hypoxia as compelling and significant. Evidence for the role of other hormones and growth factors important in leptin expression, regulation, and secretion is still emerging. Given this combinational complexity, it is easy to agree with Sierra-Johnson et al. (6) and conclude that to study the effect of altitude alone on leptin levels, confounding factors need to be controlled and considered. Factors, such as cold exposure, physical activity, diet, and genetic adaptations, as well as sleep, are sure to be important in leptin level regulation, especially given the variability of each in high-altitude exposure during a demanding activity such as mountaineering.

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circadian rhythm of leptin entry into spinal cord, however, seems to correlate with that reported in this journal for another cytokine, tumor necrosis factor-α (3). The report by Sierra-Johnson et al. (5) should stimulate examination of the effects of hypoxia on leptin transport across the BBB.

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REGULATION OF LEPTIN BY HYPOXIA

TO THE EDITOR: Leptin, as a major cytokine secreted from adipocytes, is a primary hormone in the control of food intake (2). Expression of leptin from adipocytes is regulated by body weight (or adiposity), food intake, other hormones, and hypoxia (1–3). At whole body level, loss of adiposity, loss of adiposity from an increase in energy expenditure (such as physical exercise) or decrease in energy intake (such as caloric restriction) will lead to a reduction in leptin expression in adipose tissue. This may explain leptin reduction in some studies of high altitude effects on leptin level (4). At molecular level, expression of leptin is increased by insulin and decreased by β3-adrenergic receptor signal that activates cAMP signaling pathway (3). Insulin may be involved in regulation of leptin level by food intake, which induces insulin secretion in β-cells. The cAMP signal is likely contributing to leptin reduction in physical exercise. Leptin expression may be upregulated by hypoxia. In obesity, hypoxia exists in adipose tissue and associates with leptin elevation (6). Leptin was reported as a hypoxia response gene whose transcription is induced by transcription factor HIF-1α (hypoxia inducible factor -1α; Ref. 1). However, this regulation was not confirmed in a later study where classical hypoxia response genes were induced in adipocytes (5). Therefore, it remains controversial about the role of hypoxia in the regulation of leptin expression. In response to high altitude, changes in body weight, food intake, oxygen level, body stress, and cold response may influence leptin level (4).

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TO THE EDITOR: Sierra-Johnson et al. (5) hypothesized that altitude stimulates leptin release through hypoxia-sensitive mechanisms. Besides peripheral mechanisms such as hypoxia inducible factor-1 transactivation of leptin gene promoter (2) or catecholamine inhibition of leptin gene expression through β-adrenergic receptors (1), central mechanisms may also be involved in altering circulating leptin levels. Blood-brain barrier (BBB) is a potential regulatory site for leptin transport into brain and leptin resistance. The transport system, with the transporting receptor ObRa for leptin to permeate the BBB, has limited capacity and is saturable (4). ObRa has a high level of expression in microvessels. The barrier function of neural vasculature is not static and is regulated dynamically in response to changes in the surrounding environment, such as changes in tissue oxygen concentration (3). Recently, it has been shown that hypoxia disrupts the barrier function of neural blood vessels through changes in the expression of claudin-5, a key molecule in the tight junction assembly, in endothelial cells (3). Taken together, acute hypoxia of high altitude may alter transport of leptin into brain by disrupting BBB and may be responsible for several symptoms of acute mountain sickness such as loss of appetite. Furthermore, during chronic exposure to high-altitude hypoxia, barrier properties of neural blood vessel may be reconstituted. In conclusion, central response to leptin may modulate circulating leptin levels under the circumstances of high altitude hypoxia in a time-dependent manner.

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