Letter To The Editor

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 in vitro study in which oxygen levels were not manipulated (3).

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 evidence in the literature that the jury is still out on the effect of altitude on leptin.

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TO THE EDITOR: The Viewpoint by Sierra-Johnson et al. (5) summarizes and emphasizes the conflicting reports on plasma concentrations of leptin at high altitudes. This raises the issue of the pertinence of these measurements to the loss of appetite, increased energy expenditure, and weight loss associated with leptin and high altitude in this Viewpoint. Such effects are generally considered to be mediated by the central nervous system (CNS) and do not necessarily involve leptin. Many years ago we emphasized the lack of correlation of blood levels of peptides with their biological actions in the CNS (2). The question of the role of leptin in CNS symptoms at high altitude could be resolved by examination of the effects of altitude/hypoxia on the transport of leptin across the blood-brain barrier (BBB). It has been known for more than a decade that the blood-to-brain transport of leptin is a saturable process, susceptible to physiological and pathological processes (1). This saturable permeation is largely responsible for the “leptin resistance” of obesity and is subject to a diurnal rhythm. Unfortunately, the diurnal rhythm of leptin concentrations in blood does not correlate with the diurnal rhythm of leptin transport across the BBB into brain or spinal cord (4). The
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 or 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 β3-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 ObRα for leptin to permeate the BBB, has limited capacity and is saturable (4). ObRα 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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TO THE EDITOR: As leptin is an adipocytokine that plays a key role for maintenance of body weight and energy homeostasis,