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Acute altitude-induced hypoxia suppresses plasma glucose and leptin in healthy humans

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Abstract

To examine the effects of acute altitude-induced hypoxia on the hormonal and metabolic response to ingested glucose, 8 young, healthy subjects (5 men and 3 women; age, 26 ± 2 years; body mass index, 23.1 ± 1.0 kg/m^2) performed 2 randomized trials in a hypobaric chamber where a 75-g glucose solution was ingested under simulated altitude (ALT, 4300 m) or ambient (AMB, 362 m) conditions. Plasma glucose, insulin, C-peptide, epinephrine, leptin, and lactate concentrations were measured at baseline and 30, 60, 90, and 120 minutes after glucose ingestion during both trials. Compared with AMB, the plasma glucose response to glucose ingestion was reduced during the ALT trial (P = .04). There were no differences in the insulin and C-peptide responses between trials or in insulin sensitivity based on the homeostasis model assessment of insulin resistance. Epinephrine and lactate were both elevated during the ALT trial (P < .05), whereas the plasma leptin response was reduced compared with AMB (P < .05). The data suggest that the plasma glucose response is suppressed at ALT, but this is not due to insulin per se because insulin and C-peptide levels were similar for both trials. Elevated plasma epinephrine and lactate during ALT are indicative of increased glycogenolysis, which may have masked the magnitude of the reduced glucose response. We conclude that, during acute altitude exposure, there is a rapid metabolic response that is accompanied by a shift in the hormonal milieu that appears to favor increased glucose utilization.

1. Introduction

The metabolic response to hypoxia, whether it is altitude or obesity related, has important implications for physiologic function. Travel to high altitude causes altitude sickness, which can lead to fatal complications, even in healthy individuals. Furthermore, obesity-induced hypoxia is associated with chronic obstructive sleep apnea, which was recently implicated in impaired glucose uptake and insulin resistance [1]. Earlier studies have shown that the metabolic response to hypoxia, contraction, and insulin includes an increase in glucose transport into skeletal muscle [2-5]. It is also known that insulin and hypoxia stimulate glucose transporter (GLUT) 4–mediated glucose transport via separate signaling pathways [3,6-8]. Hypoxia induces glucose uptake via a calcium-dependent and insulin-independent pathway [8,9] that, similar to exercise, involves the stimulation of GLUT4 translocation to the plasma membrane with a concomitant increase in glucose uptake [3]. In contrast, insulin-mediated glucose transport is achieved through activation of the canonical phosphatidylinositol 3-kinase pathway that stimulates a separate pool of GLUT4 glucose transporters [10-12]. Much of the research examining the effects of hypoxia on glucose metabolism has been conducted using animal models or in vitro methods [3,9,13-15]. These data show that, in dogs [14], hypoxia increases plasma glucose concentrations, whereas in vitro

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studies report up-regulation of GLUT4 protein expression and increases in glucose uptake into muscle [3,13,15]. Human studies that have examined glucose metabolism after acute exposure to hypoxia, particularly altitude-induced hypoxia, have also reported mixed results [16,17]. Thus, although there is convincing evidence from in vitro studies that the effects of insulin and hypoxia on glucose uptake in muscle are additive, in vivo data from human and animal studies are more ambiguous.

Leptin is a hormone that is synthesized and released from white adipose tissue. It functions as a lipostatic signal that acts on target receptors in the hypothalamus to lower food intake and modulate adiposity [18-20]. Leptin also plays an important role in insulin resistance by promoting fat oxidation and by inhibiting lipid synthesis [21-23]. The effects of altitude on plasma leptin are controversial [24]. There is evidence that leptin is increased during prolonged altitude exposure, and this increase may be linked to satiety and food intake [25]. This explanation is quite plausible because weight loss and reduced appetite are well-recognized features in lowlanders who ascend to altitude. However, there is also some evidence that leptin is decreased at altitude; and this response has been attributed to weight loss and changes in fat mass or, alternatively, to altitude-related increases in sympathetic drive [16,26,27].

The purpose of this study was to examine the effects of acute altitude-induced hypoxia on glucose metabolism after glucose ingestion in young healthy adults. Second, we wished to assess the effect of acute altitude-induced hypoxia on plasma hormone responses during glucose ingestion. Acute altitude exposure was achieved by a rapid 15-minute ascent to 4300 m in an altitude chamber; the subjects then remained at this altitude for the duration of the test. We hypothesized that blood glucose would be suppressed at altitude because of the combined effect of insulin and hypoxia on peripheral glucose uptake in healthy insulin-sensitive subjects and that leptin levels would be reduced in response to increased sympathetic activity induced by hypoxia. These studies provide novel data on the acute metabolic responses to altitude-induced hypoxia, independent of acclimation, obesity, insulin resistance, and/or weight loss in healthy adults.

2. Methods

2.1. Participant characteristics

Eight young, healthy, recreationally active, sea-level–dwelling adults (5 men and 3 women; age, 26 ± 2 years; body mass index, 23.1 ± 1.0 kg/m^2) volunteered to participate in the study. Each participant completed a medical history questionnaire and underwent a complete blood and urine chemistry test, medical examination, and a resting electrocardiogram. Exclusion criteria included the following: smoking, cardiovascular abnormalities, respiratory conditions, women who were pregnant, or individuals with abnormal fasting glucose. Each participant was informed of the procedures before written consent was obtained. The protocol and the consent form were approved by the Institutional Review Board of the Pennsylvania State University in accordance with the university guidelines for the protection of human subjects.

2.2. Study protocol

The protocol consisted of 2 randomized trials, one at the prevailing ambient (AMB) altitude (362 m) and one in an altitude chamber (described below) at a simulated altitude (ALT) of 4300 m. Trials were performed 1 week apart for the men, and the 2 women's trials were completed between days 3 to 8 of the follicular phase of the menstrual cycle. Subjects were instructed to eat a eucaloric diet containing at least 250 g of carbohydrates per day for the 3 days before each testing day. After a 12-hour overnight fast, subjects reported to the laboratory. Upon arrival, a polyethylene catheter was inserted into an antecubital vein, which was used for blood sampling and kept patent with 0.9% saline. Once the catheter was in place, the subject was required to recline in a supine position throughout the trial and was either brought to ALT or remained seated under AMB conditions. A baseline blood sample was drawn followed by ingestion of a 75-g glucose solution. Venous blood samples were subsequently obtained at 30, 60, 90, and 120 minutes. For each trial, the glucose load was administered by 9:00 AM.

2.3. Altitude chamber

The hypo/hyperbaric study chamber has a 35-m^3 capacity and the capability of temperature and humidity control to an altitude of 15 000 m. An attached airlock with independent pressure control was used whenever an investigator needed to enter or exit the chamber, with no variation in the study chamber equivalent altitude. In this study, participants were taken to altitude at a rate of 300 m/min; and so, it took approximately 15 minutes to reach 4300 m. At this altitude, the chamber barometric pressure and partial pressure of oxygen were approximately 446 and 95.4 mm Hg, respectively.

2.4. Blood analysis

Blood samples for glucose determination were collected in sodium heparin tubes and analyzed by the glucose oxidase method, using an automated glucose analyzer (Beckman Instruments; Fullerton, CA). Samples for insulin, C-peptide, and leptin analysis were collected in EDTA and aprotinin (Trasylol; Sigma Aldrich, St. Louis, MO) tubes. Insulin and C-peptide measurements were determined using a radioimmunoassay technique (Linco, St Charles, MO, and Diagnostic Products, Los Angeles, CA, respectively). Leptin was determined via a commercial enzyme-linked immunosorbent assay (Linco). Blood for epinephrine determination was dispensed into prechilled tubes containing ethylene glycol-*bis*(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid and

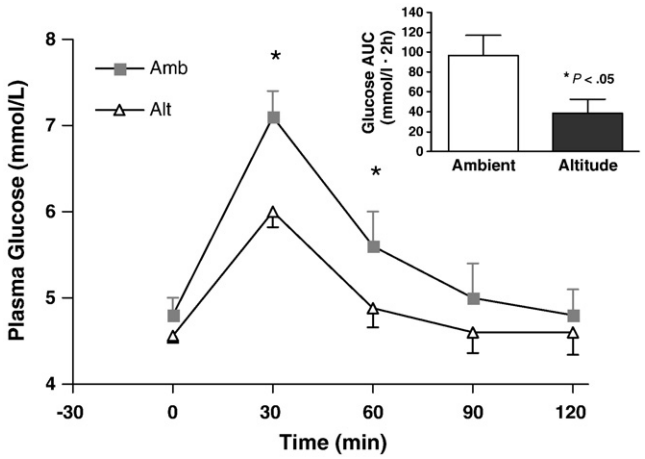

Fig. 1. Plasma glucose response at ALT and AMB. Time course for the plasma glucose response after ingesting a 75-g glucose solution. Values represent means ± SE. Closed square (■) corresponds to the AMB trial; closed triangle (△) corresponds to the altitude trial. *Significantly higher than the altitude trial, $P < .05$. Inset, AUC during the AMB and ALT trials.

reduced glutathione. Epinephrine was determined by high-performance liquid chromatography (Waters Associates, Milford, MA) using electrochromatic detection as previously described [28,29]. Samples for lactate were collected in prechilled tubes containing 1 mL of 0.7 mol/L perchloric acid, in which 0.5 mL of whole blood was dispensed and mixed. Measurement of lactate in the blood was made using a spectrophotometric method [30]. All blood samples were immediately placed on ice and then centrifuged for 10 minutes at 3000 rpm at 4°C. All plasma was separated and then stored at −80°C until analysis.

2.5. Data analysis

Repeated-measures analysis of variance and Newman-Keuls post hoc tests were used to analyze glucose, lactate, insulin, C-peptide, and epinephrine responses. Insulin sensitivity was calculated via the homeostasis model assessment of insulin resistance (HOMA-IR) (fasting glucose * fasting insulin/22.5). Area under the curve (AUC) was calculated according to the trapezoid rule. A 1-way analysis of variance was performed to determine differences between glucose, lactate, insulin, C-peptide, and epinephrine AUC for each trail. Plasma leptin data were not normally distributed and were analyzed using a Wald-Wolfowitz nonparametric test. All data are presented as the mean ± SE. The level of statistical significance was set a priori at $P < .05$.

3. Results

3.1. Baseline measurements

Baseline blood samples for each trial were analyzed to assess day-to-day variation in the metabolic measures. There were no differences in any of the plasma variables. It is evident from these data that the subjects were well controlled and in a similar metabolic state before each trial.

3.2. Glucose and lactate responses

The glucose response to the oral glucose stimulus was significantly reduced ($P = .04$) during the ALT trial as compared with the AMB, as was area under the response curve (Fig. 1). In contrast, lactate levels were significantly elevated during the ALT trial over all time points ($P = .03$, Table 1). Area under the lactate response curve was significantly increased during the ALT trial as compared with AMB ($P = .03$, Table 1).

3.3. Insulin and C-peptide responses

Insulin and C-peptide responses to the glucose solution were not different between trials (Table 1). Based on HOMA-IR, there was no difference in insulin sensitivity between trials (AMB, 37.3 ± 6.1; ALT, 31.0 ± 2.8; $P = .22$).

3.4. Epinephrine and leptin responses

Epinephrine levels were significantly elevated during the ALT trial over all time points ($P = .04$) except 90 minutes. Area under the curve was also significantly increased during the ALT trial as compared with AMB

Table 1
Plasma insulin (in picomoles per liter), C-peptide (in picomoles per liter), and lactate (in millimoles per liter) concentrations before and after glucose ingestion for the AMB and ALT trials

Variable	Baseline	30 min	60 min	90 min	120 min	AUC
Insulin						
AMB	54.4 ± 7.6	241.1 ± 62.0	225.9 ± 40.1	133.4 ± 23.3	125.3 ± 29.7	14 184 ± 3382
ALT	53.2 ± 4.0	287.8 ± 41.4	186.5 ± 31.2	136.43 ± 27.1	95.6 ± 17.2	14 007 ± 2553
C-peptide						
AMB	3.99 ± 0.71	10.31 ± 0.58	10.13 ± 0.96	9.47 ± 1.20	8.27 ± 1.17	602.3 ± 71
ALT	4.01 ± 0.62	10.97 ± 0.52	10.22 ± 0.74	10.13 ± 0.88	8.45 ± 1.02	661.6 ± 58
Lactate						
AMB	0.95 ± 0.16	1.15 ± 0.20	1.17 ± 0.13	1.18 ± 0.10	1.04 ± 0.12	20.27 ± 9.9
ALT	0.86 ± 0.14	1.37 ± 0.21*	1.47 ± 0.15*	1.36 ± 0.13*	1.23 ± 0.14*	46.87 ± 5.1*

Area under the curve (insulin and C-peptide, picomoles per liter 2 hours; lactate, millimoles per liter 2 hours). Data represent mean ± SE.
* Significantly different from AMB trial, $P < .05$.

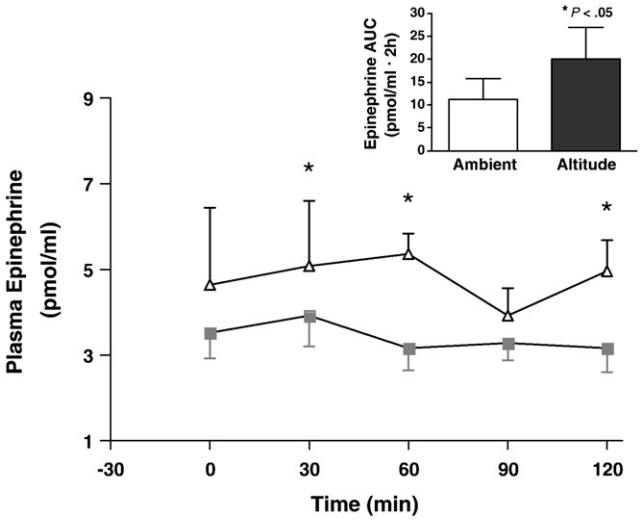

Fig. 2. Plasma epinephrine response at ALT and AMB. Time course for the plasma epinephrine response after ingesting a 75-g glucose solution. Values represent means ± SE. Closed square (■) corresponds to the AMB trial; closed triangle (△) corresponds to the altitude trial. *Significantly higher than the AMB trial, $P < .05$. Inset, AUC during the AMB and ALT trials.

($P = .02$, Fig. 2). Epinephrine and lactate showed a strong linear relationship during the ALT trial, which trended toward significance ($r = 0.79$, $P = .06$). These variables did not correlate during the AMB trial. Leptin levels were reduced in the ALT trial as compared with AMB (Fig. 3), and these differences reached statistical significance at 60 ($P = .02$) and 90 minutes ($P = .02$).

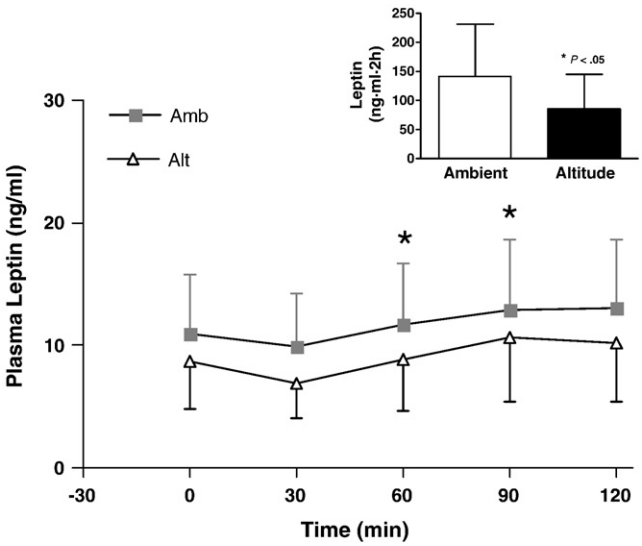

Fig. 3. Plasma leptin response at ALT and AMB. Time course for the plasma leptin response after ingesting a 75-g glucose solution. Values represent means ± SE. Closed square (■) corresponds to the AMB trial; closed triangle (△) corresponds to the altitude trial. *Significantly higher than the AMB trial, $P < .05$. Inset, AUC during the AMB and ALT trials.

4. Discussion

We proposed that acute altitude-induced hypoxia would accelerate glucose metabolism when glucose was ingested at altitude in young healthy adults. We found that a single exposure to a simulated altitude of 4300 m in lean men and women resulted in a lower glucose response after ingestion of 75 g of glucose compared with ingesting the same amount of glucose under normoxic AMB conditions. This glucose response was achieved without altering the insulin response or insulin secretion as measured by changes in C-peptide levels. These data suggest that the effects of hypoxia on glucose uptake that have been clearly demonstrated using in vitro studies also occur in vivo in healthy humans. The decrease in circulating leptin suggests that a decrease in fat utilization may be one of the coordinated metabolic responses to acute altitude/hypoxia exposure.

The reduced glucose response during altitude-induced hypoxia was not accompanied by a change in insulin sensitivity as measured by HOMA-IR. In contrast, Oltmanns et al [31] found that, after a brief 30-minute exposure to hypoxia, insulin action was impaired during a euglycemic clamp. It is likely that differences in timing and duration of exposure to hypoxia may explain these contradictory outcomes. In addition, the infusion of insulin and glucose during a clamp provides a different physiologic stimulus compared with ingestion of glucose. Although the clamp is considered the criterion standard for determining insulin action, glucose ingestion has the advantage of being more physiologic and somewhat more representative of nutrient ingestion at altitude. Furthermore, HOMA-IR, which is calculated from fasting glucose and insulin measures, accounts for hepatic and peripheral insulin sensitivity. Larsen et al [32] performed euglycemic-hyperinsulinemic clamps after 2 days of exposure to altitude and found that insulin action was impaired. However, again these data are not directly comparable because of physiologic adaptations that were occurring during the 2 days of acclimation. Euglycemic clamp studies in an altitude chamber are needed to provide a more definitive answer regarding the effects of acute altitude exposure on peripheral and hepatic insulin sensitivity.

Epinephrine inhibits peripheral insulin action [33] and insulin release during hypoxia [34-36]. However, despite elevated epinephrine levels during the ALT trial, insulin secretion and the insulin response to glucose were not different between trials. This is not surprising given that a 10-fold increase in epinephrine is necessary to elicit a decrement in peripheral insulin action [37]. Furthermore, we saw a linear trend between epinephrine and lactate during hypoxia, suggesting that epinephrine exerts its effects via increasing glycogenolysis, thereby increasing blood lactate. However, this scenario is probably limited to the muscle, as blood glucose concentrations would have increased if hepatic glycogenolysis were elevated. Insulin suppresses hepatic glucose production; and given that insulin levels

were unaltered at altitude, epinephrine's glycogenolytic actions on the liver may be overridden by the insulin response to the glucose load. Thus, the decrease in plasma glucose during the ALT trial is likely due to an increase in glucose uptake and metabolism by the muscle.

Because leptin plays an important role in regulating fat oxidation in liver and skeletal muscle [22], it is possible that the decrease in leptin during hypoxia is part of a mechanism that lowers fat oxidation. The suppressed leptin response at altitude was sustained immediately after glucose ingestion and throughout the remaining 2 hours of the trial. It is most likely that elevated epinephrine concentrations during the ALT trial contributed to this suppressed leptin response. Similar acute changes in plasma leptin in response to exercise [38] and nutritional perturbations [39] were reported previously. Therefore, although the magnitude of change in the leptin response to hypoxia may be modest, there does appear to be some capacity to alter circulating leptin under certain physiologic conditions in humans, an effect that is reproducible in different experimental settings. Such a response may make sense in the context of leptin's role in the acute regulation of hunger and satiety.

In conclusion, we have demonstrated that, in healthy young adults, plasma glucose and leptin are suppressed after glucose ingestion when compared with normal AMB conditions. These data also suggest that enhanced glucose metabolism occurs even though insulin levels are not increased and epinephrine levels are elevated. Thus, acute hypoxic exposure may have additive effects to that of insulin in regulating postprandial glucose metabolism in humans. Furthermore, lower leptin during hypoxia has the potential to reduce fat oxidation, thus providing an additional mechanism to facilitate increased glucose utilization.

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