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Erythropoiesis in women during 11 days at 4,300 m is not affected by menstrual cycle phase

J. T. Reeves, S. Zamudio, T. E. Dahms, I. Asmus, B. Braun, G. E. Butterfield, R. G. McCullough, S. R. Muza, P. B. Rock and L. G. Moore

J Appl Physiol, December 1, 2001; 91 (6): 2579-2586.

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Women at altitude: short-term exposure to hypoxia and/or α 1-adrenergic blockade reduces insulin sensitivity

B. Braun, P. B. Rock, S. Zamudio, G. E. Wolfel, R. S. Mazzeo, S. R. Muza, C. S. Fulco, L. G. Moore and G. E. Butterfield

J Appl Physiol, August 1, 2001; 91 (2): 623-631.

[Abstract] [Full Text] [PDF]

Women at altitude: carbohydrate utilization during exercise at 4,300 m

B. Braun, J. T. Mawson, S. R. Muza, S. B. Dominick, G. A. Brooks, M. A. Horning, P. B. Rock, L. G. Moore, R. S. Mazzeo, S. C. Ezeji-Okoye and G. E. Butterfield

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Women at altitude: changes in carbohydrate metabolism at 4,300-m elevation and across the menstrual cycle

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Braun, Barry, Gail E. Butterfield, Shannon B. Dominick, Stacy Zamudio, Rosann G. McCullough, Paul B. Rock, and Lorna G. Moore. Women at altitude: changes in carbohydrate metabolism at 4,300-m elevation and across the menstrual cycle. *J. Appl. Physiol.* 85(4): 1966–1973, 1998.—We hypothesized that, in women, the blood glucose response to a meal (BGR) would be lower after exposure to 4,300 m compared with sea level (SL) and that BGR would be reduced in the presence of estrogen plus progesterone (E+P) relative to estrogen alone (E). Sixteen women were studied in both the E and E+P conditions at SL and in either the E or E+P condition at 4,300 m. On *day 9* in each condition, blood was sampled before, and every 30 min for 2 h after, the subjects ate a high-carbohydrate meal. At 4,300 m, BGR peaked at a lower value (5.73 ± 0.94 mM) than at SL (6.44 ± 1.45 mM) and returned to baseline more slowly ($P < 0.05$). Plasma insulin values were the same but C peptide was slightly higher at 4,300 m ($P < 0.05$). At SL, BGR returned to baseline more slowly in E+P condition (5.13 ± 0.89 and 5.21 ± 0.91 mM at 60 and 90 min, respectively) relative to E condition (4.51 ± 0.52 and 4.69 ± 0.88 mM, respectively) ($P < 0.05$). Insulin and C peptide were not different between E and E+P conditions. The data indicate that BGR is lower in women at high altitude compared with the SL, possibly due to greater suppression of hepatic glucose production or stimulation of peripheral glucose uptake by insulin. BGR was lower in E condition relative to E+P condition at SL and possibly at 4,300 m, but the relative concentrations of ovarian hormones do not appear to alter the magnitude of the change in BGR when women are exposed to high altitude.

glucose tolerance; estrogen; progesterone; insulin sensitivity; hypobaric hypoxia; ovarian hormones

HUMAN CARBOHYDRATE METABOLISM adapts to changes in the internal (exercise training, positive or negative energy balance) and external (heat, cold, hypoxia) physiological environments. The impact of high altitude on carbohydrate metabolism in fasted and/or exercising individuals has been somewhat characterized (6, 19, 31; see Refs. 4, 5 for reviews), but the effects of high altitude on the metabolic response to a meal have rarely been studied, even though more than one-third of daily life is spent in the postprandial condition. The available data indicate that the blood glucose response to oral or intravenous carbohydrate is lower after chronic exposure to high altitude than it is at sea level, but these studies have only been done in men (16, 28, 29, 34). Interpretation of these data is confounded by weight loss in the test subjects, which is difficult to avoid at high altitudes and independently

lowers the glucose response to a meal (17). A greater ambient insulin concentration and/or higher rates of insulin secretion (as indicated by elevated plasma C-peptide levels) could be responsible for a lower blood glucose response at altitude, but, to date, no studies of postmeal glucose metabolism at high altitude have included measurements of plasma insulin or C-peptide concentrations. In the one study that included women, only fasting glucose concentrations were measured (19).

There are credible reasons to anticipate that exposure to high altitude will affect carbohydrate metabolism differently in women than in men (3). In addition to other gender differences (adiposity, fat distribution, testosterone, etc.), there are direct and indirect effects of the ovarian hormones estrogen (E) and progesterone (P) on pathways of intermediary metabolism (7, 22, 32, 33). Postprandial glucose metabolism, as assessed by measuring glucose tolerance and/or insulin sensitivity, is reported to be somewhat impaired in the luteal phase of the cycle (when E and P are both relatively abundant) relative to the follicular phase (when E is high but P is low) (12, 14, 15, 20), although no difference between phases has also been observed (12, 35, 36). If the relative concentrations of the ovarian hormones alter carbohydrate metabolism, the effects of high altitude exposure in women may vary depending on which cycle phase they are in when they are being studied.

We hypothesized that, as observed in men (16, 28, 29, 34), the blood glucose response to a high-carbohydrate meal would be lower in women at high altitude relative to the response at sea level. We anticipated that the reduction in blood glucose response would occur in the absence of a systematic change in plasma insulin secretion or concentration, because fasting insulin levels reported in male subjects were similar to sea level values (4, 6, 23, 31). Furthermore, we speculated that, because enhancement of insulin sensitivity may be blunted by P (7, 13, 14, 18, 21, 22), the magnitude of the change in blood glucose response to altitude would be diminished in the presence of E and P (characteristic of the luteal phase of the menstrual cycle) relative to the response to E alone (characteristic of the follicular phase). To test these hypotheses, we compared glucose, insulin, and C-peptide responses to a high-carbohydrate meal in young women, in both phases of the menstrual cycle, at sea level and after 9 days of exposure to 4,300-m elevation.

METHODS

Study design. As part of a multifaceted study of how young women acclimatize to high altitude, we measured the blood glucose response to a standardized meal twice at sea level and again after 9 days exposure to 4,300 m.

Subjects. Eighteen women, 21–34 yr old, completed the sea level portion of this study. Because of illness, two of the women did not perform the studies at high altitude. All of the women were sea-level residents (<1,500-m elevation), non-smoking, with regular menstrual cycles (see detailed description of menstrual cycle in *Menstrual cycle-phase determinations*). All subjects were in good overall health on the basis of a routine physical examination and were in the clinically normal range for standard blood and urine chemistry panels, including hemoglobin and serum ferritin. They had normal fasting and 2-h postprandial blood glucose concentrations. Subjects all reported being moderately to very physically active and underwent a standard graded exercise test to peak O₂ uptake on a cycle ergometer (Monark). Subject characteristics are shown in Table 1. The women gave written consent to participate before the start of the study, and the protocol was approved by institutional review boards of all of the participating institutions.

Sea-level and high-altitude conditions. At sea level (Palo Alto, CA = 15-m elevation), subjects were studied for 12 days on each of two occasions, usually ~6 wk apart. Subjects were free living on *nights 1–6* and slept in the metabolic ward on *nights 7–11* of each study period. One to 3 mo after the sea-level studies, subjects were flown to Colorado Springs (elevation 6,200 feet) and driven by car to Pikes Peak, Colorado, arriving at the summit (4,300 m = 14,110 feet) 2 h later. On Pikes Peak, women were housed in the Maher Memorial Laboratory for the 12-day study period. Room temperature was controlled between 19 and 23°C at both Pikes Peak and Palo Alto. In each of the three study periods, the blood glucose response to a standardized meal was measured on the morning of *day 9* (31 tests) ± 1 day (9 tests). *Day 9* was chosen to represent the altitude-acclimatized state because many of the metabolic adaptations (metabolic rate, catecholamine concentrations, glucoregulatory hormones) occur in the first 7 days of altitude exposure and have plateaued at stable levels by *day 9* (4, 5, 25).

Menstrual cycle-phase determinations. To control the impact of menstrual cycle phase on the effect of altitude to change the blood glucose response, subjects were studied in both cycle phases at sea level so that the test at high altitude

could be compared with the corresponding sea-level test. Testing subjects in both phases at sea level also allowed us to compare the blood glucose response to the test meal between menstrual cycle phases, with each subject serving as her own control.

To ensure that testing occurred in the appropriate phase at the appropriate time, each subject kept a menstrual cycle diary noting the date of her menses, the date of a surge in luteinizing hormone (LH; monitored with an ovulation predictor kit from OvuQuick, Becton-Dickson, Rutherford, NJ), and duration of the cycle. *Day 1* of each study period at sea level and high altitude was the day after menses began (beginning of the follicular phase) or the day after an LH surge was detected (beginning of the luteal phase). After the study was completed, menstrual diaries, body temperature profiles, and, most importantly, serum concentrations of the ovarian hormones E and P (collected on the morning of *days 9* or *10* within 1 day of the standardized meal test) were reviewed. Ovarian hormone concentrations are shown in Table 1. In 10 cases, women had abnormal phases as defined by low concentrations of either E (below the normal clinical range of 10 pg/ml in the follicular phase or 10 pg/ml in the luteal phase) or P (never exceeding 2.4 pg/ml in the luteal phase). Statistical comparison of the absolute hormone concentrations in these cases did not differ from those of women with documented normal follicular phases. We included the data collected in the 10 abnormal cases with those measured during the follicular phase, because most of the available evidence indicates that absolute and relative blood concentrations of the ovarian hormones are mainly responsible for mediating cycle-related effects on intermediary metabolism (18). Because this decision oversimplifies the complex interactions that characterize the follicular and luteal cycle phases, we refer to the two conditions according to the ovarian hormone environment: E alone (E condition) or E plus P (E+P condition). We believe this terminology is more consistent with one of the main study objectives: to understand how the ovarian hormones influence the regulation of carbohydrate metabolism.

On the basis of post hoc hormone analysis described above, 12 subjects completed all of the sea level tests and could appropriately be compared between the E and E+P conditions. Although equal numbers of subjects were scheduled to arrive at high altitude in the E and E+P conditions, only five subjects had P concentrations indicative of a normal luteal phase. Because each subject had a corresponding sea-level test, all 16 subjects could be compared between sea level and high altitude within the ovarian hormone condition.

Test meal At ~7:30 AM, after an overnight fast, a baseline blood sample was collected without stasis via an indwelling catheter inserted into an antecubital vein. Immediately after this procedure, subjects consumed a test meal within 10–15 min [English muffin, jelly, margarine, Ensure liquid formula (Ross Laboratories, Columbus, OH)] that contained 2,064 kJ (493 kcal) and was composed of 69% carbohydrate, 10% protein, and 21% fat. Total carbohydrate content was 84 g, which is comparable to the 75–100 g consumed in a standard glucose tolerance test. Venous blood samples were collected 30, 60, 90, and 120 min after the meal ended and assayed for glucose, insulin, and C-peptide concentrations. Plasma insulin concentrations were determined to assess whether the ambient insulin level, a potential modulator of the blood glucose response (11), varied between elevations or cycle phases. C peptide was measured because it is cosecreted into the portal vein in equimolar concentrations with insulin, but, unlike insulin, almost all of the secreted C peptide appears in the general circulation, so plasma concentrations of C peptide

Table 1. *Subject characteristics*

	Sea Level (12)	4,300 m (16)	
		E ₂ only (11)	E + P (5)
Age, yr	21.7 ± 2.0	22.1 ± 1.8	21.1 ± 1.6
Height, cm	167.4 ± 4.4	167.0 ± 4.0	168.1 ± 4.1
Weight, kg	62.2 ± 4.0	60.9 ± 4.5	66.3 ± 11.0
VO _{2peak} , ml · kg ⁻¹ · min ⁻¹	42.0 ± 5.9	31.9 ± 4.2	30.8 ± 5.7
E, pg/ml			
F	50.8 ± 7.6	80 ± 59	83 ± 39
L	95.7 ± 32.2		
P, ng/ml			
F	0.43 ± 0.10	0.8 ± 0.3	5.7 ± 6.1
L	7.66 ± 4.65		

Values are means ± SD; nos. in parentheses are no. of subjects. E, serum concentration of estrogen; P, serum concentration of progesterone; VO_{2peak}, peak O₂ uptake; F, follicular phase; L, luteal phase. E and P were measured the day of the metabolic tests, *day 9* or *10* of the cycle phase.

are more sensitive indicators of insulin secretion than is insulin itself.

To minimize the effects of changes in energy balance, body weight and carbohydrate intake on meal tolerance, subjects consumed the same tightly controlled, standardized diet every day of each 12-day study period. Energy content of the diet was adjusted daily to maintain body weight. Approximately 64% of kilocalories came from carbohydrate, 12% from protein, and 24% from fat. Energy intake at 4,300 m was initially set at the sea-level intake required for weight maintenance. Basal metabolic rate was measured daily, and energy intake was adjusted to compensate for any changes, with additional energy provided to maintain body weight if necessary. Detailed descriptions of the energy content of the diet and the use of dietary control to obviate weight loss at altitude have been published previously (8). Careful attention to energy balance resulted in no significant change in body weight during days 1–12 at sea level (0.0 kg) or 4,300 m (-0.5 ± 0.1 kg).

Biochemical assays. Blood samples used for ovarian hormone determinations were allowed to clot at room temperature for 30 min and were centrifuged at 3,000 rpm for 10 min, and serum was transferred to a cryogenic vial and stored at -80°C until analysis. Serum aliquots were assayed for E and P concentrations by using Coat-A-Count radioimmunoassay kits (Diagnostic Products, Los Angeles, CA). For estradiol, the assay sensitivity was 8 pg/ml. Within- and between-day precision was 6 and 11%, respectively. For P, sensitivity was 0.2 ng/ml and within- and between-day precision was 8 and 12%, respectively.

Blood samples used for determination of glucose, insulin, and C peptide were centrifuged at 3,000 rpm for 10 min, and plasma was transferred to cryogenic vials and frozen at -20°C (glucose) or -80°C (insulin, C peptide) until analysis. Plasma glucose concentrations were determined by the glucose oxidase method by using a CHEM1 analyzer. Concentrations of insulin and C peptide in plasma were measured by competitive binding by using Coat-A-Count radioimmunoassay kits and double-antibody radioimmunoassay kits (both from Diagnostic Products), respectively. For insulin, the assay sensitivity was 30 pmol/l. Between-day precision was 13%. For C peptide, sensitivity was 0.1 nmol/l and between-day precision was 9%.

Statistical analysis. Data in the text and Table 1 are presented as means \pm SD. Figures show means \pm SE for visual clarity. Statistical comparisons among group means were made with a two-way analysis of variance (ovarian hormone condition \times time, elevation \times time) with repeated measures (repeated-measures ANOVA). Testing the interaction of ovarian hormone condition on altitude exposure (ovarian hormone condition \times elevation \times time) was complicated by the skewed distribution between sea level (8 E, 8 E+P) and high altitude (11 E, 5 E+P). This comparison was made with the Wilcoxon signed-rank nonparametric test. Tukey's Studentized range test was used to compare individual time points when significant ($P < 0.05$) F -ratios were obtained.

RESULTS

Results are presented under three main categories to address the specific questions addressed in this study.

1) Effects of altitude with ovarian hormone condition controlled. The plasma glucose, insulin, and C-peptide responses to the test meal were compared between sea level and high altitude (4,300 m). Comparisons were made within a single ovarian hormone condition, with

11 subjects in E condition at both sea level and 4,300 m and 5 in E+P condition. The fasting plasma glucose concentration was slightly (+4.7%) but significantly higher at 4,300 m compared with sea level (Fig. 1). The pattern of change after the meal was significantly different between conditions; plasma glucose peaked at a lower value (5.73 ± 0.94 mM) at 4,300 m relative to sea level (6.44 ± 1.45 mM; $P < 0.05$). After 60 min, plasma glucose was 11% below baseline at 4,300 m but still elevated by 8% over baseline at sea level ($P < 0.01$). There were no differences between conditions 90 and 120 min postmeal. To determine whether differences in ambient insulin levels accounted for the change in glucose response, plasma insulin concentrations were measured. Fasting insulin concentrations were exactly the same at sea level and 4,300 m (Fig. 2A). The pattern of change over time (8-fold increase at 30 min followed by decline toward baseline) after the meal was also identical in both conditions. Plasma C-peptide concentrations were determined to assess whether differences in insulin secretion could be affecting the blood glucose responses to the meal. Fasting concentrations of C peptide were 27% higher at 4,300 m relative to sea level ($P < 0.01$; Fig. 2B). C-peptide levels increased approximately equally under both conditions (3.5- to 4-fold) but returned toward baseline more slowly at 4,300 m so that plasma C-peptide concentrations were significantly higher 120 min postmeal compared with sea level ($P < 0.05$).

2) Effects of ovarian hormone condition with each subject as her own control. The plasma glucose, insulin, and C-peptide responses to the test meal were compared between the E and E+P conditions at sea level. Fasting glucose concentrations were slightly but significantly lower (5%; $P < 0.05$) in E+P compared with E conditions (Fig. 3). In response to the meal, plasma glucose concentrations peaked at the same value in

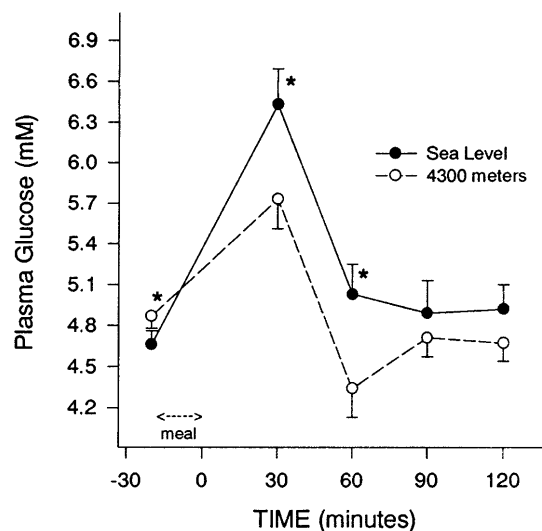


Fig. 1. Plasma glucose concentrations before and after a high-carbohydrate meal at sea level and 4,300 m. Values are means \pm SE; $n = 16$ subjects. Subjects were studied in the same ovarian hormone condition at each elevation [11 estrogen (E), 5 estrogen plus progesterone (E+P)]. *Significant differences at individual time points, $P < 0.05$.

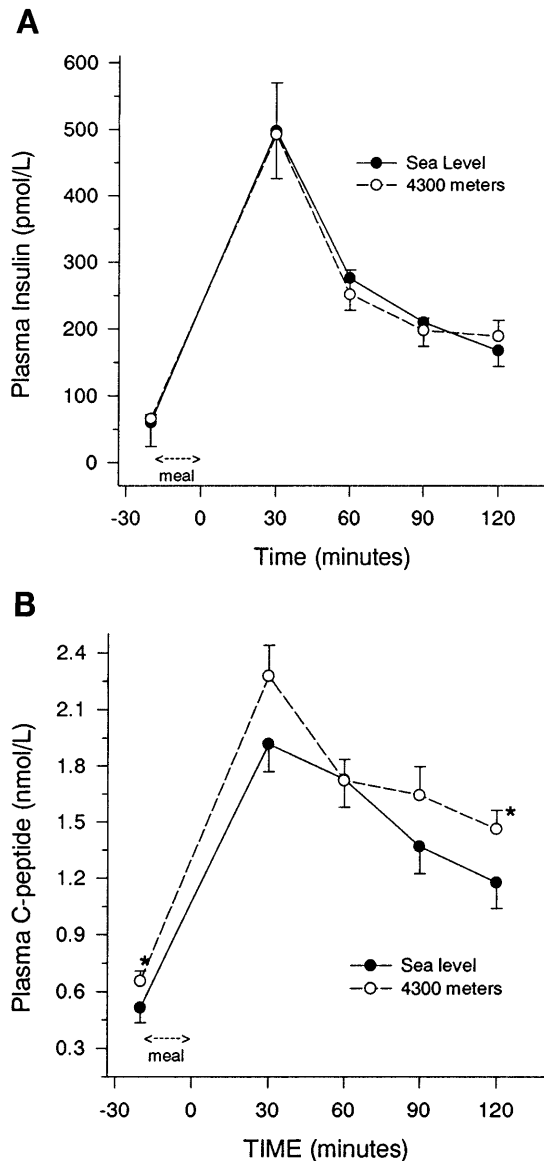


Fig. 2. Plasma insulin (A) and C-peptide (B) concentrations before and after a high-carbohydrate meal at sea level and 4,300 m. Values are means \pm SE; $n = 16$ subjects.

both cycle phases but fell more slowly in the luteal phase. Glucose concentrations had returned to baseline by 60 min in E but were still significantly elevated above baseline at 60 and 90 min in E+P conditions ($P < 0.05$). Fasting plasma insulin concentrations and the plasma insulin response to the meal were practically identical between conditions (Fig. 4A), rising seven- and ninefold by 30 min postmeal in E and E+P, respectively, and returning almost to baseline by 120 min. Fasting concentration of C peptide in plasma was the same in E and E+P (Fig. 4B). In response to the meal, C-peptide levels rose ~ 3.5 -fold at 30 min in both conditions. The rate of return toward baseline was the same between E and E+P.

3) *The interaction between ovarian hormone condition and elevation.* Testing the effects of ovarian hormone condition on the blood glucose response to a meal at 4,300 m was complicated by an unequal distribution

of cycle phases at altitude (Fig. 5). For illustrative purposes, the cycle-induced change in blood glucose response [defined as follows: (area under the blood glucose curve in the luteal phase) – (area under the blood glucose curve in the follicular phase)] is shown at sea level and 4,300 m (Fig. 6). Statistical comparison by using a nonparametric test did not show any difference between conditions.

DISCUSSION

In young women, the glucose response to a high-carbohydrate meal was considerably reduced after 9 days of exposure to high altitude compared with their response at sea level. The change in blood glucose response occurred in the absence of differences in plasma insulin concentration, although there was a subtle increase in plasma C-peptide concentrations at 4,300 m relative to sea level. At sea level, plasma glucose response to the meal peaked at a similar concentration but returned to baseline significantly more slowly in E compared with E+P conditions. At 4,300 m, data looked almost identical to the pattern observed at sea level, but direct comparison was difficult with only 5 of 16 subjects in the E+P condition. Plasma insulin and C-peptide responses to the meal were the same in both ovarian hormone conditions.

Higher fasting glucose concentrations were noted after 9 days at 4,300 m, which is the opposite of some, but not all, observations in men exposed to high altitude and in high-altitude natives (4–6, 33). Although statistically significant, the small magnitude of the difference (+0.15 mM) is probably not physiologically relevant.

Lower peak glucose concentrations, and a faster return to baseline values, in response to a high-carbohydrate meal at 4,300 m are consistent with all of the studies performed on men (16, 28, 29, 34). In our study, subjects were weight stable during the stay at

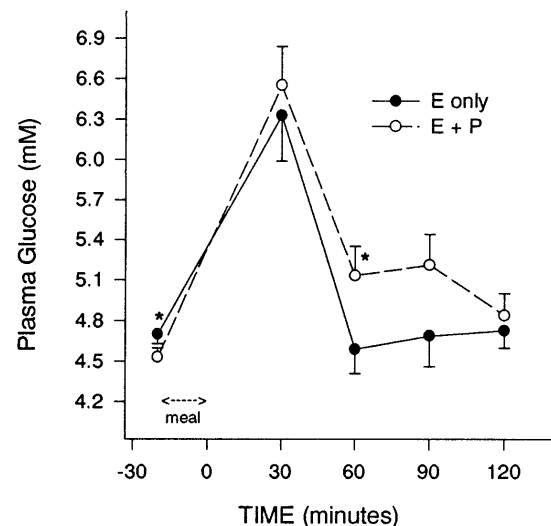


Fig. 3. Plasma glucose concentrations before and after a high-carbohydrate meal in E and E+P conditions at sea level. Values are means \pm SE; $n = 12$. * Significant differences between conditions, $P < 0.05$.

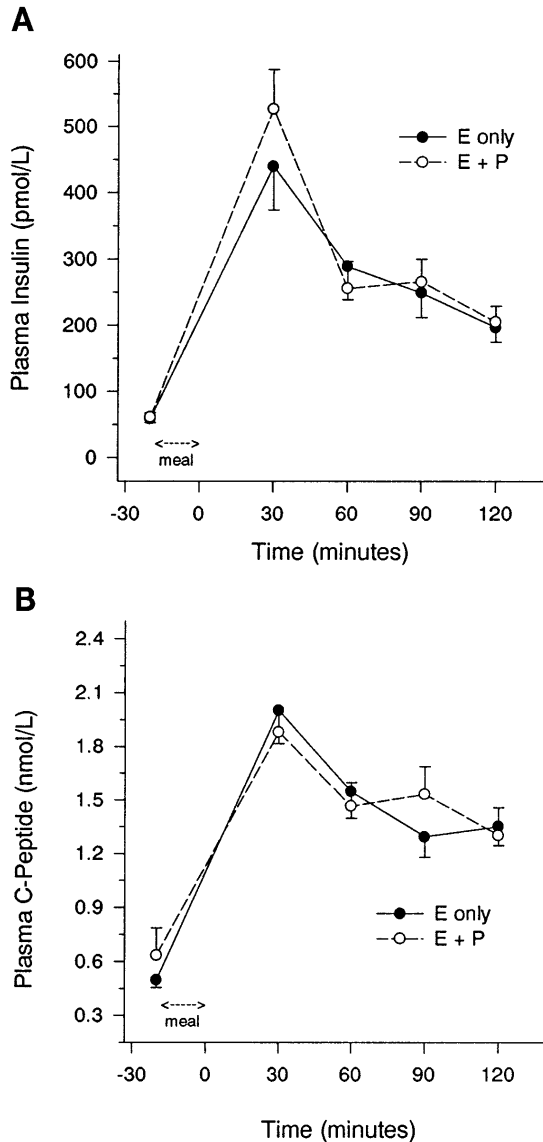


Fig. 4. Plasma insulin (A) and C-peptide (B) concentrations before and after a high-carbohydrate meal in E and E+P conditions at sea level. Values are means \pm SE; $n = 12$ subjects.

high altitude, implying that the change in glucose metabolism is a true response to altitude hypoxia per se and not an artifact of altitude-associated weight loss. The lower blood glucose response at high altitude could be explained by several physiological changes. Carbohydrate absorption by the gastrointestinal system could be delayed or reduced. Although this is theoretically possible, Chesner (10) found no evidence for carbohydrate malabsorption in men exposed to 3,100- and 4,800-m elevation. Partial depletion of liver glycogen could reduce glucose output by the liver and contribute to the lower glucose response, particularly for individuals consuming inadequate amounts of energy and/or carbohydrate. Subjects in the present study, however, were fed energy adequate to maintain energy balance, and, given the composition of the diet (69% of energy from carbohydrate), it is unlikely that depletion of liver glycogen explains our findings.

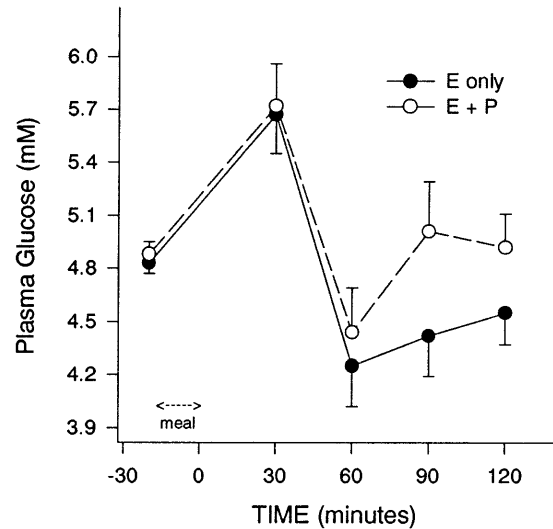


Fig. 5. Plasma glucose concentrations before and after a high-carbohydrate meal in E ($n = 11$) and E+P ($n = 5$) conditions at 4,300 m. Values are means \pm SE.

In men, epinephrine and norepinephrine are acutely elevated on ascent to high altitude and remain elevated after 9 days of exposure (24). In the present study, plasma epinephrine and norepinephrine concentrations were elevated by 25% ($P < 0.05$) and 28% [not significant (NS)], with urinary epinephrine and norepinephrine levels 23% (NS) and 111% ($P < 0.05$) higher, after 10 days at 4,300 m compared with sea level (25). An acute effect of elevated catecholamines is to stimulate hepatic glucose production and restrain insulin release (mainly mediated by actions of the α -adrenergic receptors), resulting in elevated blood glucose concentrations (30). Over time, however, chronically elevated catecholamines can enhance insulin production (a response to the elevated blood glucose and compensatory action of β -adrenergic receptors) (30). The net effects in

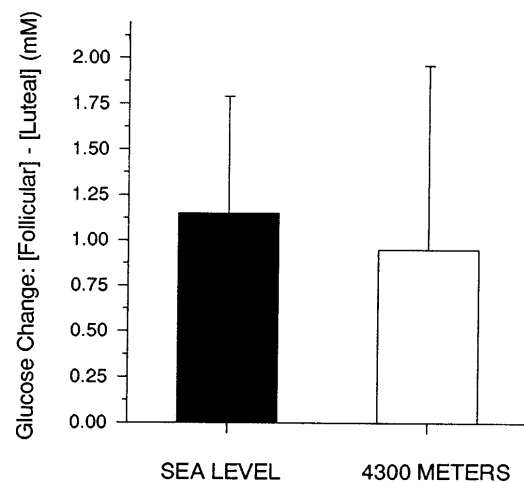


Fig. 6. Change in total blood glucose response to a meal across ovarian hormone condition [defined as follows: (area under the curve in E+P) - (area under the curve in E)] at sea level ($n = 12$ in both E and E+P) and 4,300 m ($n = 16$, 11 E and 5 E+P). Values are means \pm SE. [Follicular] and [luteal], glucose concentration in follicular and luteal phase, respectively.

altitude-acclimatized individuals are glucose and insulin concentrations that differ little from sea-level values (slightly lower blood glucose at altitude has sometimes been observed) (4, 5). Therefore, it seems more likely that changes in insulin action, rather than concentration, underlie the alterations in postmeal carbohydrate metabolism seen after exposure to high altitude.

The blood glucose response could be lower because glucose uptake from the blood is increased as a result of enhanced sensitivity of peripheral tissues (primarily muscle and fat) to insulin. In vitro, hypoxia was reported to increase glucose uptake in both normal (9) and insulin-resistant (1) skeletal muscle. Blood glucose uptake during exercise is increased at 4,300 m relative to uptake at sea level (4–6, 31), and, although glucose uptake during exercise is mainly regulated by muscle contractions rather than by insulin, this finding does support the concept that glucose is taken up from the blood more readily at high altitude. Not all data are confirmatory, however. Larsen et al. (23) directly measured insulin sensitivity in men with a euglycemic, hyperinsulinemic-clamp technique at sea level and 4,559 m. During the clamps, constant infusion of insulin raised plasma insulin concentrations 12- to 15-fold over fasted levels, but plasma glucose concentrations were held equal to the fasted state by variable rates of glucose infusion. Glucose uptake rates were 55% lower after 2 days at 4,559 m relative to sea level. Glucose uptake rates had returned more than halfway to baseline after 7 days at 4,559 m and may have returned to (or even exceeded) sea-level values after longer acclimatization. Also, because the euglycemic clamp completely suppresses hepatic glucose production (HGP), the method does not measure the effects of hypoxia on suppression of HGP by insulin. Increased hepatic insulin sensitivity at high altitude would lower HGP, reducing the total glucose load (ingested glucose plus glucose output from the liver) entering the blood after a meal, and lower the blood glucose response.

Surprisingly, although plasma insulin concentrations were the same at sea level and 4,300 m, plasma C-peptide concentrations were somewhat greater at high altitude. These data imply that insulin secretion was increased at high altitude, but more rapid insulin clearance resulted in no net change in insulin levels in the blood. Insulin clearance is mainly regulated by the liver, and alterations in the hepatic insulin clearance rate are not well understood. In support of our data, lower plasma insulin concentrations were noted by Larsen et al. during their euglycemic clamp protocol after 7 days at 4,559 m (23). With endogenous insulin production suppressed and each subject receiving the same amount of exogenous insulin, lower plasma insulin concentrations at high altitude also suggest an increased rate of insulin clearance. If a greater portion of secreted insulin is removed by the liver before it reaches the general circulation at high altitude compared with sea level, it could result in a greater suppression of HGP, lowering the total glucose load as

noted above, with no apparent change in the prevailing plasma insulin concentration.

One of the questions we attempted to address was the importance of the relative concentrations of the ovarian hormones on the blood glucose response to high altitude. The potential relevance of this question was borne out by our finding that the blood glucose response to a meal was lower in the presence of E alone relative to E+P at sea level in our group of subjects. The effect of ovarian hormones and menstrual cycle phase on glucose metabolism has a long and controversial history in the literature (see Ref. 18 for excellent review), with reports both showing a difference between follicular and luteal phases (13–15, 20, 27) or no effect of cycle phase (12, 35, 36).

Two consistent patterns permeate and may explain the discrepant literature. First, study methods that acutely raise the plasma glucose concentration, such as glucose consumption (present study and Refs. 14, 15, 20, 27) or a hyperglycemic clamp (13), tend to show that glucose metabolism is somewhat impaired during the luteal relative to the follicular phase. However, if plasma glucose concentrations are held at fasting levels (euglycemic clamp), there is usually no effect of menstrual cycle phase (12, 35, 36). Because elevated glucose concentrations can suppress liver glucose production independent of the effects of insulin (2), greater suppression of HGP by the rise in blood glucose after a meal (or a hyperglycemic clamp) during the follicular relative to the luteal phase could explain the results of studies like ours. Complete suppression of HGP by supraphysiological insulin concentrations during a euglycemic clamp may render the technique insensitive to changes in glucose production that underlie menstrual cycle-phase variation.

Second, the concentration of serum P attained during the luteal phase in the subject population may skew the observed results. In a report by Toth et al. (no cycle-phase difference), serum P only increased from 0.2 ng/ml in the follicular phase to 4.4 ng/ml in luteal (35). In a study by Diamond et al. (12) (major differences across cycle phase), serum P rose from 0.2 ng/ml (follicular phase) to 20.3 ng/ml (luteal phase), and the authors found a significant inverse correlation ($r = 0.66$) between the change in serum P and the change in glucose uptake. Kalkhoff (21) reported independent effects of exogenous P impaired insulin-mediated glucose uptake in five men and two hysterectomized women. Assuming serum P is important in determining carbohydrate tolerance, the increase in serum P from 0.4 (E) to 7.7 ng/ml (E+P) in the present study may have been sufficient to tease apart subtle differences between cycle phases. We did not find a significant correlation, however, between the P concentration in E+P condition and the increase in blood glucose response in the luteal phase ($r = 0.53$, $P > 0.05$), although, if one subject was excluded from the analysis (highest P concentration but no change in glucose response across cycle phase), the relationship improved to $r = 0.70$ and $P = 0.08$. A potential relationship between peak P levels in the luteal phase and decre-

ment in glucose tolerance and insulin sensitivity merits further study.

Reduced insulin sensitivity in the luteal phase constituted the rationale for hypothesizing that magnitude of the blood glucose response to altitude would be greater in E relative to E+P conditions. This hypothesis could not be adequately addressed. The beginning of each study period was dictated by biology rather than convenience. Although we planned to test an equal number of subjects in E and E+P conditions at 4,300 m, only five subjects were actually studied in E+P. Nonparametric analysis of the data showed no trend toward an effect of cycle phase on the altitude-induced reduction in blood glucose response.

In conclusion, the blood glucose response to a high-carbohydrate meal is lower after 9 days at high altitude than at sea level in young women. The effects of altitude are not dependent on changes in plasma insulin concentration but may be related to differences in insulin secretion and clearance. It is likely that whole-body insulin sensitivity is enhanced after chronic exposure to high altitude, but whether this change is the result of additive or opposing changes in peripheral and hepatic insulin sensitivity requires further study. The relative concentrations of E and P affect glucose metabolism, but their impact appears to be consistent at sea level and high altitude. As long as subjects are tested within the same cycle phase, the choice of phase is unlikely to alter the results. The application of these data to altitude effects in general is constrained by the length of altitude exposure in this study. We report changes in carbohydrate metabolism that occurred after 9 days at high altitude (when subjects were partly to mostly acclimatized) relative to sea level. The acute effects of high-altitude exposure may be very different.

The practical relevance of a lower blood glucose response to a meal at high altitude to an individual vacationing or working in the mountains depends on the underlying mechanisms. If individuals are more insulin-sensitive at high altitudes, substrate selection may shift toward greater oxidation of carbohydrate (see Refs. 4–6 for data in men) and it may be important to ensure that the diet consumed is rich in carbohydrates. Conversely, if the effects noted are attributable to a greater suppression of glucose output by the liver after a meal, carbohydrate use might be lower in women at high altitude with a greater reliance on nonglucose fuel sources (3). In the latter scenario, consumption of a high-carbohydrate diet would be less important. Studies that address the mechanisms by which glucose metabolism is regulated at high altitude are necessary to distinguish between the possibilities.

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