Women at altitude: short-term exposure to hypoxia and/or $\alpha_1$-adrenergic blockade reduces insulin sensitivity

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Received 27 July 2000; accepted in final form 23 March 2001

Women at altitude: short-term exposure to hypoxia and/or $\alpha_1$-adrenergic blockade reduces insulin sensitivity. J Appl Physiol 91: 623–631, 2001.—After short-term exposure to high altitude (HA), men appear to be less sensitive to insulin than at sea level (SL). We hypothesized that the same would be true in women, that reduced insulin sensitivity would be directly related to the rise in plasma epinephrine concentrations at altitude, and that the addition of $\alpha_1$-adrenergic blockade would potentiate the reduction. To test the hypotheses, 12 women consumed a high-carbohydrate meal at SL and after 16 h at simulated 4,300-m elevation (HA). Subjects were studied twice at each elevation: once with prazosin (Prz), an $\alpha_1$-adrenergic antagonist, and once with placebo (Pla). Mathematical models were used to assess insulin resistance based on fasting [homeostasis model assessment of insulin resistance (HOMA-IR)] and postprandial [composite model insulin sensitivity index (C-ISI)] glucose and insulin concentrations. Relative to SL-Pla (HOMA-IR: 1.86 ± 0.35), insulin resistance was greater in HA-Pla (3.00 ± 0.45; P < 0.05), SL-Prz (3.46 ± 0.51; P < 0.01), and HA-Prz (2.82 ± 0.43; P < 0.05). Insulin sensitivity was reduced in HA-Pla (C-ISI: 4.41 ± 1.03; P < 0.01), SL-Prz (5.73 ± 1.01; P < 0.05), and HA-Prz (4.18 ± 0.99; P < 0.01) relative to SL-Pla (8.02 ± 0.92). Plasma epinephrine was significantly elevated in HA-Pla (0.57 ± 0.08 ng/ml; P < 0.01), SL-Prz (0.42 ± 0.07; P < 0.05), and HA-Prz (0.82 ± 0.07; P < 0.01) relative to SL-Pla (0.28 ± 0.04), but correlations with HOMA-IR, HOMA-$\beta$-cell function, and C-ISI were weak. In women, short-term exposure to simulated HA reduced insulin sensitivity compared with SL. The change does not appear to be directly mediated by a concurrent rise in plasma epinephrine concentrations.

homeostatic model; glucose tolerance; insulin resistance; epinephrine; prazosin

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uals become acclimatized, epinephrine levels fall back to sea-level values. Blood concentrations of norepinephrine, however, increase slowly and remain elevated for at least 3 wk (25–27). In one report, chronic exposure to high levels of norepinephrine induced by continuous infusion was reported to enhance sensitivity to insulin (22). Based on these data, short-term exposure to high-altitude hypoxia may result in a hormonal environment, characterized by a relatively high concentration of epinephrine with little or no change in norepinephrine, which is conducive to diminished insulin sensitivity (insulin resistance).

We hypothesized that, relative to sea level, short-term exposure to high-altitude hypoxia in women would reduce insulin sensitivity. We measured insulin sensitivity using mathematical modeling techniques that incorporate fasting concentrations of glucose and insulin and their responses to ingested carbohydrate. In addition, to test a secondary hypothesis, we took advantage of a concurrent study in which this group of women was given a drug (prazosin) designed to selectively block the α1-adrenergic limb of the sympathetic nervous system. We anticipated that α1-adrenergic blockade would exaggerate the rise in epinephrine at high altitude and potentiate the insulin resistance engendered by hypoxia alone.

**METHODS**

**Study design.** To test the hypotheses, we measured the glucose and insulin responses to a high-carbohydrate meal in four conditions and used mathematical models to evaluate insulin sensitivity and β-cell function. Each subject performed the tests at sea level (barometric pressure = 760 mmHg) and then at simulated 4,300-m elevation (barometric pressure = 454 mmHg), once while taking the α1-adrenergic antagonist prazosin and once while taking placebo (double-blind, order of drug or placebo treatments balanced across subjects).

**Subjects.** The protocol was approved by institutional review boards of all participating institutions before the start of the study, and, after being familiarized with the procedures, all subjects gave written consent to participate. Fifteen women volunteered for the study, but three were unable to complete the testing in one or both of the high-altitude conditions, and their incomplete data were excluded from the analysis. Twelve women (mean age = 24.7 ± 1.3 yr, height = 169.2 ± 2.2 cm, weight = 70.82 ± 2.77 kg at sea level) completed the study. Those women were sea-level residents (<1,500-m elevation), nonsmoking, and in good overall health based on a health history and physical examination. They had regular menstrual cycles based on self-reports, measurements of basal body temperature, and hormonal analysis detailed below. Subjects were in the clinically normal range for thyroxin, hemoglobin, and serum ferritin. They had normal fasting and 2-h postprandial blood glucose concentrations. Subjects reported being slightly-to-moderately physically active and had a mean peak \( O_2 \) uptake = 33.7 ± 2.17 mg·kg\(^{-1}\)·min\(^{-1}\) measured on a cycle ergometer.

**Sea-level and high-altitude conditions.** At sea level (Natick, MA), subjects entered the hypobaric chamber at 4:00 PM on day 1. They lived there, with the doors open to ambient air at a sea-level barometric pressure of ~760 mmHg, for 68 h. At 12:00 noon on day 4, the doors were sealed, and the chamber was depressurized to 446 ± 1 mmHg (the barometric pressure at 4,300 m) over the next 10 min. Room temperature and humidity were controlled at 19 ± 2°C and 40 ± 5%, respectively. Subjects remained under these conditions for 52 h (4:00 PM on day 6), when the chamber was repressurized.

**α-Adrenergic antagonist.** During one of their two testing periods, subjects took 1.0 mg of prazosin, a short-acting, selective α1-adrenergic antagonist, three times per day by mouth. In the other testing period, subjects received an identical-looking placebo. A phenylephrine challenge (incremental infusion of phenylephrine, an α-agonist, at increasing dosage until systolic blood pressure >20 mmHg over baseline) was used to assess the degree of blockade on day 3 at sea level. The phenylephrine dose required to raise systolic blood pressure >20 mmHg above baseline increased from 2.0 ± 0.3 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) in the placebo condition to 10.7 ± 2.0 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) when the subjects were taking prazosin (\( P < 0.001 \)), indicating substantial α1-adrenergic blockade.

**Carbohydrate tolerance test.** After 16 h at either sea level or 4,300 m, the last 10–12 h of which were in a fasting state, a baseline blood sample was collected without stasis via an indwelling catheter inserted into an antecubital vein at least 30 min earlier. Immediately after the baseline sample, subjects had 10–15 min to consume a high-carbohydrate meal (English muffin, jelly, margarine, orange juice, Ensure liquid formula [Ross Laboratories, Columbus, OH]) that contained 2,064 kJ (493 kcal) and was composed of 69% carbohydrate, 10% protein, and 20% fat. Total carbohydrate content was 84 g, which is comparable to the 75 g consumed in a standard glucose tolerance test, and results in a similar blood glucose response (4). Absorption of macronutrients does not appear to be affected at altitudes <5,500 m (18, 35). 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, varied between elevations. C-peptide was measured as an adjunct measure of insulin secretion.

**Biochemical assays.** Samples of venous blood were collected in tubes containing either 7% HClO\(_4\) (for analysis of glucose) or 100 μg aprotinin (Trasylol, Sigma Chemical) as a protease inhibitor (for analyses of insulin and C peptide). All samples were immediately stirred with a vortex mixer and kept ice cold until they were centrifuged at 3,000 rpm for 10 min, and the 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 using a CHEM1 analyzer and corrected for perchloric acid dilution. Concentrations of insulin and C peptide in plasma were measured by competitive binding using Coat-A-Count radioimmunoassay kits and double-antibody radioimmunoassay kits (Diagnostic Products, Los Angeles, CA), respectively.

**Mathematical models.** Glucose and insulin concentrations were used to calculate indexes of insulin sensitivity with the use of two different mathematical models. The first, homeostasis model assessment (HOMA), allows quantitative assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-BCF) using fasting concentrations of glucose and insulin according to the formula

\[
\text{HOMA-IR} = \frac{\text{FPI}}{\text{FPG}} \times 22.5
\]

where FPI and FPG are the fasting (plasma) insulin and glucose concentrations in μU/ml and mmol/l, respectively, and...
HOMA-BCF \(= 20 \times \frac{FPI}{FPG} - 3.5\) \(2\)

The formulas are based on an array of predicted glucose and insulin values that would be expected for many potential combinations of \(\beta\)-cell deficiency and insulin resistance \(24\). A very insulin-sensitive reference individual with normal \(\beta\)-cell function would be described by values of HOMA-IR = 1.0 and HOMA-BCF = 100\%. Individuals with some degree of relative insulin resistance (HOMA-IR > 1.0) can be further characterized according to whether they are hyperinsulinemic (HOMA-BCF \(\geq 100\%\)) or insulin-deficient (HOMA-BCF \(< 100\%)\). For example, in the San Antonio Heart Study, a very large group of Caucasian men and women with normal glucose tolerance was reported to have a HOMA-IR of \(2.1 \pm 0.1\); whereas those with impaired glucose tolerance and non-insulin-dependent diabetes mellitus had values of \(4.3 \pm 0.5\) and \(8.3 \pm 0.7\), respectively \(15\). HOMA-IR and -BCF were shown to be extremely reproducible and very well correlated with data obtained using the euglycemic hyperinsulinemic clamp, the hyperglycemic clamp, and continuous infusion of glucose with model assessment \(11, 17, 24\).

Matsuda and DeFronzo \(23\) recently developed a dynamic model designed to assess insulin sensitivity in the nonfasting state. The model incorporates both fasting values and the glucose and insulin responses to oral glucose into a whole body insulin sensitivity index termed the “composite model” (C-ISI). The C-ISI is calculated according to the formula

\[ \frac{10,000}{(FPG \times FPI)} \times (MPG \times MPI) \]  

where MPG and MPI are the mean plasma glucose and insulin concentrations, respectively, during a 120-min oral glucose tolerance test.

The C-ISI encompasses a range from 12 (very sensitive) to 1 (extremely resistant) and is very well correlated with total body glucose disposal rate per unit insulin measured during euglycemic clamps in subjects with normal glucose tolerance, impaired glucose tolerance, and non-insulin-dependent diabetes mellitus \(22\). Although the C-ISI was developed for use with a liquid glucose solution rather than a solid meal, there is good reason to believe that it can be appropriately applied to the very high glycemic index meal used in the present study. The meal was extremely high in carbohydrate (70\% of energy, mainly composed of simple sugars) and low in fiber and fat and produces a blood sugar and insulin profile very similar to that observed in response to a standard oral glucose tolerance test \(2\). Our laboratory has previously shown that the magnitude of an exercise-induced change in sensitivity to insulin is almost identical whether measured by the plasma glucose response to an insulin/glucose infusion or by the glucose and insulin responses to a similar high-carbohydrate meal \(4\).

**Menstrual cycle phase determinations.** To control for the confounding effects of performing metabolic tests across phases of the menstrual cycle, the study was designed so that each subject would be studied within a given cycle phase. To ensure that testing occurred 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 (monitored with an ovulation predictor kit from OvuQuick, Becton-Dickson, Rutherford, NJ), and duration of the cycle. After the study was completed, menstrual diaries and serum concentrations of the ovarian hormones estrogen and progesterone were reviewed. All 13 subjects were in the same cycle phase when tested in the sea-level and high-altitude conditions. When tested in the placebo and prazosin conditions, nine subjects were in the same phase (5 in follicular, 3 in luteal, 1 menstruating). Three subjects were in the luteal phase during placebo but the follicular phase during prazosin, and one was tested in the reverse situation.

**Dietary control.** The use of dietary control to obviate weight loss at altitude has been described previously \(7\). To minimize the effects of changes in energy balance and carbohydrate intake on metabolic parameters, subjects consumed the same standardized diet every day. Approximately 64\% of kcal 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. However, subjects were not always able to consume adequate energy to maintain energy balance at altitude because of loss of appetite and other symptoms associated with acute mountain sickness (AMS). Based on analysis of dietary records, we estimate that energy intake was \(\sim 84 \pm 3\%\) of calculated energy requirements during the 2 days at high altitude, and subjects lost 1.38 \(\pm 0.8\) kg body wt.

AMS. To evaluate the potential impact of AMS on carbohydrate metabolism, the cerebral component of AMS (AMS-C) was assessed every morning and evening using scores on the Environmental Symptoms Questionnaire. AMS-C scores were assigned severity index values to allow comparison among individuals \(33\) and were stratified into tertiles (severity index \(\leq 1 = \text{AMS-C} \leq 1.530; 2 = 1.531 \leq \text{AMS-C} \leq 2.080; 3 = \text{AMS-C} \geq 2.081\)). Subjects with severity index 3 were considered “sick,” and those with severity index 1 were classified as “well.” Before the carbohydrate tolerance test, seven subjects were well and four were sick in the placebo condition, compared with six well and five sick on prazosin. Statistical analysis. Group data are presented as means \(\pm SE\). Statistical comparisons between group means (sea-level placebo (SL-Pla), sea-level prazosin (SL-Prz), high-altitude placebo (HA-Pla), and high-altitude prazosin (HA-Prz)) were made with a two-way analysis of variance with repeated measures. When significant \(F\) ratios \((P < 0.05)\) were detected, paired \(t\)-tests were used to make post hoc comparisons. As recommended by Curran-Everett et al. \(10\), comparisons among groups are presented as the difference between group means \((\Delta)\), the 95\% confidence interval, and the exact \(P\) value. Significant differences between group means are defined by confidence intervals that do not include zero and that also show the magnitude and direction of the differences. Pearson product-moment correlation analysis was used to assess whether there was any relationship between plasma epinephrine concentrations and indexes of insulin sensitivity. To test the influence of AMS on glucose tolerance at altitude, severity indexes based on AMS-C scores were segregated into tertiles, and the upper and lower tertiles were compared using an unpaired \(t\)-test.

**RESULTS**

**Fasting state.** Relative to the SL-Pla condition, the plasma glucose concentration was significantly higher with altitude alone (HA-Pla) and with prazosin alone (SL-Prz) (Fig. 1 and Table 1). There was also a significant rise in plasma glucose when altitude and prazosin were combined (HA-Prz) that was equal in magnitude to the HA-Pla. The plasma insulin concentration in the fasting state was not significantly higher after HA-Pla \((P = 0.056)\) and was not altered by SL-Prz (Fig. 2A and Table 1). The combined intervention (HA-Prz) resulted in a significant rise. C-peptide concentrations in the fasting state were not significantly different among conditions.
In the SL-Pla condition, HOMA-IR was $1.86 \pm 0.35$ (Table 2). Relative to SL-Pla, HOMA-IR was significantly higher (61%) with HA-Pla. With prazosin only (SL-Prz), there was a significant increase of almost twofold compared with SL-Pla. With both treatments (HA-Prz), the combined effect was approximately the same as with altitude exposure alone.

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Responses to the meal. Plasma glucose concentrations rose to a peak at 30 min and returned to (SL-Pla) or toward (all others) baseline by 120 min (Fig. 1). As shown in Table 1, glucose incremental area under the curve (AUC) was greater with altitude exposure alone (HA-Pla). The glucose AUC was also increased with prazosin alone (SL-Prz), and, in conjunction with altitude exposure (HA-Prz), the rise was particularly pronounced.

In response to the meal, plasma insulin concentrations peaked at 30 min in all conditions and did not return completely to baseline by 120 min (Fig. 2A). Insulin AUC was markedly increased by HA-Pla. Prazosin alone had no effect on insulin AUC at sea level (SL-Prz) and did not alter the altitude-induced rise in insulin AUC when combined with high-altitude exposure (HA-Prz).

The peak concentrations of C peptide occurred 30 min postmeal and were still elevated above the baseline at 120 min (Fig. 2B). Altitude alone (HA-Pla) significantly raised the plasma C-peptide AUC. There was no effect of SL-Prz, but, in combination with alti-

Table 1. Effects of altitude alone, prazosin alone, and both treatments on plasma glucose, insulin, and C peptide before (0 min) and in responses to (area under the curve) a standard meal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control (SL-Pla)</th>
<th>Altitude only (HA-Pla)</th>
<th>Prazosin only (SL-Prz)</th>
<th>Altitude + prazosin (HA-Prz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose at 0 min, mM</td>
<td>4.71 ± 0.13</td>
<td>4.93 ± 0.14</td>
<td>5.08 ± 0.10</td>
<td>5.09 ± 0.15</td>
</tr>
<tr>
<td>Δ from SL-Pla</td>
<td>0.23</td>
<td>-0.06 to 0.49</td>
<td>0.13 to 0.60</td>
<td>0.01 to 0.74</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.115</td>
<td>0.006*</td>
<td>0.045*</td>
<td>0.045*</td>
</tr>
<tr>
<td>Glucose AUC, mM/min</td>
<td>93.5 ± 23.0</td>
<td>167.3 ± 16.9</td>
<td>146.0 ± 22.7</td>
<td>204.7 ± 24.0</td>
</tr>
<tr>
<td>Δ from SL-Pla</td>
<td>73.8</td>
<td>8.3 to 96.7</td>
<td>79.2 to 159.2</td>
<td>111.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>28.2 to 119.4</td>
<td>0.018*</td>
<td>0.041*</td>
<td>0.018*</td>
</tr>
<tr>
<td>Exact P value</td>
<td>0.015*</td>
<td>0.015*</td>
<td>0.015*</td>
<td>0.015*</td>
</tr>
<tr>
<td>Insulin at 0 min, pM</td>
<td>23 ± 3</td>
<td>35 ± 4</td>
<td>34 ± 5</td>
<td>35 ± 4</td>
</tr>
<tr>
<td>Δ from PLP-z</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>95% CI</td>
<td>-1 to 25</td>
<td>-3 to 27</td>
<td>1 to 24</td>
<td>1 to 24</td>
</tr>
<tr>
<td>Exact P value</td>
<td>0.056</td>
<td>0.099</td>
<td>0.099</td>
<td>0.099</td>
</tr>
<tr>
<td>Insulin AUC, nM/min</td>
<td>18.1 ± 3.2</td>
<td>41.9 ± 11.0</td>
<td>21.8 ± 4.5</td>
<td>43.9 ± 9.2</td>
</tr>
<tr>
<td>Δ from SL-Pla</td>
<td>23.8</td>
<td>3.7</td>
<td>25.8</td>
<td>25.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>8.1 to 39.5</td>
<td>-2.2 to 9.6</td>
<td>10.6 to 41.0</td>
<td>10.6 to 41.0</td>
</tr>
<tr>
<td>Exact P value</td>
<td>0.021*</td>
<td>0.305</td>
<td>0.016*</td>
<td>0.016*</td>
</tr>
<tr>
<td>C peptide at 0 min, nM</td>
<td>0.89 ± 0.12</td>
<td>1.07 ± 0.10</td>
<td>1.05 ± 0.10</td>
<td>1.10 ± 0.11</td>
</tr>
<tr>
<td>Δ from SL-Pla</td>
<td>0.18</td>
<td>0.16</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.12</td>
<td>0.16</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>Exact P value</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>C-peptide AUC, nM/min</td>
<td>220 ± 17</td>
<td>282 ± 16</td>
<td>224 ± 21</td>
<td>296 ± 21</td>
</tr>
<tr>
<td>Δ from SL-Pla</td>
<td>62</td>
<td>4</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>95% CI</td>
<td>29 to 95</td>
<td>-4 to 4</td>
<td>28 to 114</td>
<td>28 to 114</td>
</tr>
<tr>
<td>Exact P value</td>
<td>0.006</td>
<td>0.875</td>
<td>0.011</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Values are means ± SE. SL, sea level; Pla, placebo; HA, high altitude; Prz, prazosin; Δ, group mean difference; CI, confidence interval; AUC, area under the curve; ns, no significant difference among groups detected by repeated-measures ANOVA and, therefore, no post hoc testing; n/a, not applicable. *Statistically significant difference from SL-Pla condition.
tude (HA-Prz), C-peptide AUC was significantly elevated and slightly potentiated compared with HA-Pla.

In SL-Pla, the C-ISI, incorporating glucose and insulin responses to the meal in addition to fasting measures, was 8.02 ± 0.92, a value corresponding to the high end of the range reported for individuals of varying glucose tolerance (22) (Table 2). There was a significant decline in C-ISI (−45%) with hypoxia alone (HA-Pla). At sea level, prazosin (SL-Prz) also lowered C-ISI, although the magnitude of the increase was smaller (−28%). The significant decrement in C-ISI (−48%) observed when α-blockade was added to hypoxia (HA-Prz) was almost identical to that seen with HA-Pla.

**Insulin sensitivity and plasma epinephrine.** Plasma epinephrine and norepinephrine concentrations in the four conditions are shown in Table 3. The relationship between the change in plasma epinephrine concentrations on exposure to hypoxia, α-blockade, or both and the change in HOMA-IR, HOMA-BCF, and C-ISI had correlation coefficients of $r = 0.31$ ($P = 0.411$) for HOMA-IR, $r = 0.22$ ($P = 0.536$) for HOMA-BCF, and $r = −0.16$ ($P = 0.733$) for C-ISI.

**Effects of AMS on glucose metabolism.** Fasting glucose concentrations and the glucose response to a meal for well (AMS-C severity index ≤1) and sick (AMS-C severity index ≥3) subjects are shown in Table 4. The presence of AMS had no significant effect on fasting glucose concentration. The plasma glucose response to a meal was always slightly higher in sick compared with well subjects, but none of the differences was significant. The same result was seen when sick vs. well subjects were subdivided and compared within the placebo or prazosin conditions.

**DISCUSSION**

Relative to normoxia, 16 h of exposure to hypobaric hypoxia reduced insulin sensitivity as measured by mathematically modeling glucose and insulin concentrations in the fasting state and in response to a high-carbohydrate meal. In normoxia, α-adrenergic blockade also tended to reduce insulin sensitivity, but, when combined with hypoxia, the effects were generally very similar to those observed with hypoxia alone. β-Cell function tended to be higher during hypoxia and was not affected by α-blockade alone or in combination with hypoxia. The changes in sensitivity to insulin and β-cell function were not consistent with the alterations in blood epinephrine concentrations during hypoxia and α-blockade.

Several confounding variables could potentially affect the results that we obtained. Insulin sensitivity can be altered by changes in short-term energy balance (29), the ovarian hormone environment (2, 14), and potentially AMS. To try and maintain neutral energy balance, diets were meticulously constructed for each subject based on measured basal metabolic rate and estimates of physical activity. The physical stress of rapid “ascent” from 760 to 458 mmHg caused moderate to severe symptoms of AMS in some subjects and at least some discomfort in the remainder. As a result, mean energy intake was only 84 ± 3% of calculated energy requirements in the hypoxic condition. Although relatively large changes (fasting, massive overfeeding) in short-term energy balance can affect insulin sensitivity, the small decrement that we observed over a very short period of time make it unlikely that our finding of reduced sensitivity to insulin during hypoxia results from energy deficit.

There is a subtle, but often measurable, effect of menstrual cycle phase on insulin sensitivity (2, 14). To help control for this variable, the study was designed so that all measurements would occur in the same menstrual cycle phase. That goal was achieved in making
comparisons between sea level and high altitude, and in 9 of 13 subjects in comparing the placebo and prazosin conditions. On three occasions, a subject was tested during the luteal phase in the placebo trial and the follicular phase in the prazosin trial, and in the reverse situation on one occasion. The subtle effect of menstrual cycle phase on insulin sensitivity, the small number of subjects involved, and the almost universal findings that insulin sensitivity is reduced in the luteal phase (which would mainly oppose our findings of higher insulin sensitivity in the placebo condition when more of the subjects were luteal) make it very unlikely that menstrual cycle phase was an important confounding variable in our results.

The presence of moderate-to-severe AMS the morning of the meal tolerance tests in approximately one-third (4 of 13 placebo, 5 of 13 blocked) of the subjects could also have influenced the results. Larsen et al. (20) found that the peak in AMS (day 2) coincided with markedly reduced sensitivity to insulin, which returned toward (although not to) sea-level values by day 7, when symptoms of AMS had disappeared (20). We explicitly tested whether, compared with individuals without symptoms, subjects with moderate-to-severe AMS had higher glucose or insulin concentrations before or in response to the meal. We found no significant effects at any time point, although blood glucose values were always slightly higher in the AMS group. The change induced by AMS (mean of 0.33 ± 0.12 mM from 30–120 min) was considerably smaller, however, than the effect of hypoxia to increase the glucose response (0.99 ± 0.20 mM).

Fasting situation. Use of HOMA-BCF showed that, compared with the SL-Pla condition, insulin secretion was greater in response to altitude exposure alone or in combination with prazosin. Unlike a standard measure of plasma insulin concentration, the HOMA-BCF incorporates fasting glucose levels into the model and, therefore, assesses the insulin secretory response scaled to the prevailing plasma glucose concentration. A caveat in the use of this model is that the measurement assumes no change in the rate of insulin clearance, and so all effects are attributed to insulin secretion. Although there are no convincing data to suggest that insulin clearance is markedly altered by hypoxia or prazosin, it is possible that subtle changes in clearance impact on the HOMA-BCF measurements. The data suggest that altitude exposure alone, or in conjunction with prazosin, increases the insulin secretory response to the plasma glucose signal and that this rise is approximately equal between those two conditions. Other investigators working at roughly similar elevations (3,500–4,550 m) have observed small elevations in plasma insulin concentrations after short-term (48–72 h) altitude residence (5, 20, 34).

A greater insulin concentration for a given plasma glucose concentration suggests some degree of insulin resistance. Results generated using the HOMA-IR are entirely consistent with that line of reasoning. HOMA-IR was significantly elevated with altitude or prazosin, it is possible that subtle changes in clearance impact on the HOMA-BCF measurements. The data suggest that altitude exposure alone, or in conjunction with prazosin, increases the insulin secretory response to the plasma glucose signal and that this rise is approximately equal between those two conditions. Other investigators working at roughly similar elevations (3,500–4,550 m) have observed small elevations in plasma insulin concentrations after short-term (48–72 h) altitude residence (5, 20, 34).

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compared our results with those obtained in the San Antonio Heart Study (15). Results from our SL-Pla condition (HOMA-IR = 1.86 ± 0.35), measured under fasting conditions, are entirely consistent with their reported value of 2.1 ± 0.1 for Caucasian subjects (men and women) with normal glucose tolerance. In response to the interventions, we observed increases in HOMA-IR to values of 3.0–3.5, which is somewhat lower than the value of 4.3 that they report for subjects with impaired glucose tolerance. Although this comparison is speculative, it appears that the fasting insulin resistance induced by altitude exposure and/or prazosin is about one-half of what would be expected in a group of individuals with clinically defined impaired glucose tolerance. The magnitude of the effect was similar with either altitude or prazosin, but there was no additive response to the combined intervention. It is possible that the two interventions alter fasting glucose metabolism via the same mechanism. Alternatively, the redundant systems of glucoregulatory machinery (e.g., greater insulin-to-glucagon ratio) may act to preserve glucose homeostasis by buffering perturbations in the plasma glucose concentration within a fairly narrow range.

Responses to the meal. When glucose and insulin concentrations in response to the meal were incorporated with the fasting levels into the C-ISI, we found a significant decline in sensitivity to insulin with each of the three interventions. The decline was less pronounced with prazosin at sea level (−28%) than after altitude exposure alone (−45%) or with prazosin (−48%). The correlation between C-ISI and glucose clamp-derived total body glucose disposal (r = 0.73, P < 0.0001) reported by Matsuda and DeFronzo (23) can be used to place these changes into a more familiar context. In the SL-Pla condition, the C-ISI of 8.02 corresponds to a glucose disposal rate of \(~5\) mg·m⁻²·μU insulin⁻¹·ml⁻¹, which is near the upper part of the normal range. The lower values seen after altitude exposure with or without prazosin are approximately equivalent to a glucose disposal rate of \(~3\) mg·m⁻²·μU insulin⁻¹·ml⁻¹, which is in the lower end of the normal range, just above the cluster of values from individuals with impaired glucose tolerance. Both fasting and postprandial data, therefore, support an acute reduction in insulin action with either short-term altitude exposure or α₁-adrenergic receptor blockade.

The altitude findings support the marked reduction in insulin sensitivity reported by Larsen et al. (20), who used the glucose clamp technique to study a group of men who spent 48 h at 4,550 m. In that study, the rate of glucose disposal in response to a steady-state level of plasma insulin was reduced by ~50%, in remarkable agreement with the results that we obtained in this study of women exposed to a similar barometric pressure. The concord between the studies implies that there are no obvious gender differences in the effects of short-term hypoxia on sensitivity to insulin.

Insulin resistance on short-term exposure, however, contrasts sharply with a lower glucose response to ingested or infused carbohydrate previously seen in men (13, 30, 31) or women (2) after altitude acclimatization. In women, our laboratory reported a lower glucose response to carbohydrate after 9 days of acclimatization to 4,300 m relative to sea level (2). The plasma insulin response was identical to sea-level values in the acclimatized women, suggesting, as others have postulated with respect to men (5, 6, 32), that insulin sensitivity was enhanced after altitude acclimatization. The only data that directly address the effects of acclimatization come from Larsen et al. (20), who found that the greatly reduced insulin sensitivity that they observed after 2 days at 4,550 m had returned almost to sea-level values after 7 days. Like the study on acclimatized women, the investigators ensured that energy intake matched energy expenditure in their subjects so that enhanced insulin sensitivity was not a function of negative energy balance. Taken together, the data suggest that there is a transition from reduced to increased sensitivity to insulin as individuals acclimatize to hypoxia over the course of ~7–10 days.

There are many mechanisms that could potentially explain the transition, but the most probable involve a change in tissue glucose uptake and/or hepatic glucose production (HGP) as a result of the direct or indirect effects of one or several of the counterregulatory hormones. Based on their study in men, Larsen et al. (20) suggested that changes in plasma cortisol during the course of acclimatization might explain at least some of their data. In our laboratory’s previous study in women, however, cortisol levels at rest did not vary much from sea-level values (3). Concentrations of growth hormone (not measured in the present study) could also be a factor. Although the changes were not

### Table 4. Effects of acute mountain sickness on fasting glucose concentration and the glucose response to a meal at 4,300 m

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Glucose Concentration, mM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Subjects</td>
</tr>
<tr>
<td>0</td>
<td>5.04 ± 0.16</td>
</tr>
<tr>
<td>30</td>
<td>7.39 ± 0.37</td>
</tr>
<tr>
<td>60</td>
<td>6.20 ± 0.39</td>
</tr>
<tr>
<td>90</td>
<td>6.41 ± 0.43</td>
</tr>
<tr>
<td>120</td>
<td>6.10 ± 0.45</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 13 well subjects and 9 sick subjects. See text for explanations of “well” and “sick.”
Epinephrine, which increases muscle glycogenolysis and hepatic glucose output and raises blood glucose concentrations, increases sharply on short-term altitude exposure but returns to sea-level values by 6–7 days (25–27). In contrast, norepinephrine concentrations have been reported to remain at sea-level values for 2–3 days at high altitude and then rise progressively for at least a couple of weeks (25–27). Although the main rationale for administering the α-adrenergic antagonist prazosin to the subjects in the present study was to assess its impact on hemodynamic parameters during acclimatization, the intervention was also a convenient tool to probe the potential impact of the catecholamines on insulin sensitivity. Because of their well-known counterregulatory actions, it was expected that, as catecholamine concentrations increased, insulin resistance would rise as well.

Partial blockade of the α-adrenergic limb of the sympathetic nervous system with prazosin was expected to greatly diminish the physiological influence of norepinephrine. We also anticipated that a compensatory increase in epinephrine concentrations (1, 28) might occur. This increase could potentiate the effect (if any) of epinephrine on insulin sensitivity. Prazosin was reported to raise the blood glucose response to glucose infusion in both rats (12) and humans (21). Although few data are available to decipher the mechanism by which this occurs, it is not likely to be explained by a lack of direct α1-adrenoceptor stimulation. Insulin secretion is responsive to α-stimulation, but it appears to be exclusively regulated via α2-receptors, which should not be affected by administration of prazosin, a selective α1-antagonist. The α-adrenergic limb of the sympathetic nervous system has also been repeatedly shown to have only a weak role in regulating carbohydrate metabolism (8, 21). It is, therefore, likely that any counterregulatory effects of prazosin are due to a compensatory rise in epinephrine, as some other investigators have reported (1, 28).

In the present study, group mean epinephrine concentrations were elevated by prazosin administration at sea level, and, with altitude exposure, the combined effect on mean epinephrine levels was almost exactly the arithmetic sum of either intervention alone. The HOMA-IR, HOMA-BCF, and C-ISI group mean results, however, all showed no effects of prazosin with altitude that exceed those attributable to altitude alone. Using the individual data, all of the correlations between changes in epinephrine concentrations and changes in HOMA-IR, HOMA-BCF, or C-ISI were weak ($r < 0.35$) and not significant. Therefore, it seems unlikely that the rise in serum epinephrine concentrations per se is a main determinant of the reduction in sensitivity to insulin observed in response to short-term hypoxia. The possibility that indirect actions of epinephrine play a role in modulating the response to hypoxia, perhaps by differentially stimulating adipose lipolysis and muscle or liver glycogenolysis, cannot be discounted. An increase in the blood concentrations of free fatty acids and/or ketones could be at least partially responsible for the exaggerated blood glucose response observed in response to hypoxia and/or α-blockade in the present study.

To decipher the regulatory mechanisms involved in modulating insulin sensitivity before and after acclimatization, it is vital to understand what portion of the effects noted are due to changes in tissue glucose uptake, which is mainly a function of peripheral insulin sensitivity, vs. HGP, which is more a result of hepatic insulin sensitivity. In men, investigators have reported increases (6, 32) and no change (20) in HGP in the resting condition after short-term altitude (4,300–4,550 m) exposure. After acclimatization, Roberts et al. (32) found that HGP was reduced relative to the acute exposure (but still higher than at sea level), and, in women, our laboratory reported that HGP was significantly lower than sea-level values after 10 days at 4,300 m (3). Larsen et al. (20) attributed their finding of reduced insulin sensitivity in men at high altitude to a decrease in peripheral insulin sensitivity. Because the infusion of glucose and insulin during their glucose clamp measurements completely suppressed HGP to zero at any elevation, it is not possible to rule out changes in hepatic sensitivity to insulin as a potential regulatory site. Use of techniques that allow partitioning of insulin sensitivity into hepatic and peripheral components (e.g., multistage hyperglycemic clamps, more sophisticated modeling of the glucose and insulin responses to oral or infused glucose) is necessary to more fully understand the acute and acclimatized responses to hypoxia.

Conclusions. Short-term exposure to an ambient oxygen content equivalent to 4,300-m elevation reduced insulin sensitivity in women. These results contrast with previous data suggesting that insulin sensitivity is enhanced in women after altitude acclimatization. The transition from reduced to enhanced sensitivity to insulin during acclimatization in women is consistent with the reported data in men. Use of an α-adrenergic antagonist independently reduced insulin sensitivity but had no additive effect in combination with hypoxia. Taken together, these data suggest that the acute effects of hypoxia on glucose metabolism are not due to the direct actions of increased epinephrine concentrations.

We acknowledge the enthusiastic cooperation of the subjects in this study. We also received valuable assistance from Rossann McCullough, Sharon Moynihan, and Leah Holloway at the Palo Alto Veterans Affairs Health Care System; and Janet Staab, MSgt. Mark Sharp, Sgt. James Kenney, and the hypobaric chamber operating crew at the US Army Research Institute of Environmental Medicine, Ross Laboratories, Hershey, and Shaklee contributed components of the diet.

This study was supported by Department of Defense Grant DAMD-17-95-C-5110.
REFERENCES


J Appl Physiol • VOL 91 • AUGUST 2001 • www.jap.org