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Effect of beta-adrenergic blockade on plasma lactate concentration during exercise at high altitude

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Summary. When unacclimatized lowlanders exercise at high altitude, blood lactate concentration rises higher than at sea level, but lactate accumulation is attenuated after acclimatization. These responses could result from the effects of acute and chronic hypoxia on β-adrenergic stimulation. In this investigation, the effects of β-adrenergic blockade on blood lactate and other metabolites were studied in lowland residents during 30 min of steady-state exercise at sea level and on days 3, 8, and 20 of residence at 4300 m. Starting 3 days before ascent and through day 15 at high altitude, six men received propranolol (80 mg three times daily) and six received placebo. Plasma lactate accumulation was reduced in propranolol- but not placebo-treated subjects during exercise on day 3 at high altitude compared to sea-level exercise of the same percentage maximal oxygen uptake ($\dot{V}O_{2max}$). Plasma lactate accumulation exercise on day 20 at high altitude was reduced in both placebo- and propranolol-treated subjects compared to exercise of the same percentage $\dot{V}O_{2max}$ performed at sea level. The blunted lactate accumulation during exercise on day 20 at high altitude was associated with reduced muscle glycogen utilization. Thus, increased plasma lactate accumulation in unacclimatized lowlanders exercising at high altitude appears to be due to increased β-adrenergic stimulation. However, acclimatization-induced changes in muscle glycogen utilization and plasma lactate accumulation are not adaptations to chronically increased β-adrenergic activity.

Key words: Acclimatization - Altitude - Hypoxia - Catecholamines - Propranolol

Introduction

Blood lactate concentration during exercise at a given intensity rises higher during acute high-altitude exposure than during similar exercise at sea level. With altitude acclimatization, the rise in lactate during exercise is attenuated (Bender et al. 1989; Edwards 1936; Young et al. 1982a, b). The mechanism for this adaptation is unknown. Recent findings indicate that a change in the availability of oxygen to the contracting muscle is not a factor (Bender et al. 1989). However, changes in blood lactate during exercise at high altitude could be mediated by circulating norepinephrine, epinephrine, or both acting on β-adrenergic receptors.

Norepinephrine and epinephrine both influence energy metabolism by stimulating β-adrenergic receptors in muscle and adipose tissue. Concentrations of these catecholamines during rest and exercise are affected by both acute high-altitude exposure and altitude acclimatization. Resting norepinephrine levels in blood and urine of lowlanders acclimatizing at high altitude have been observed to increase, while resting epinephrine concentrations remained at sea-level values (Cunningham et al. 1965). During exercise, however, blood epinephrine levels increase as a result of acute high-altitude exposure while the concentration of norepinephrine remain at sea-level values. Altitude acclimatization has been reported to attenuate both plasma epinephrine and norepinephrine responses to exercise (Mazzeo et al. 1989). These alterations in circulating catecholamine levels could mediate the glycolytic (Gregg et al. 1989; Mazzeo and Marshall 1989; Wiener and Taylor 1985) and lipolytic (Rosell 1966) responses observed during exercise at high altitude.

The aim of the present investigation was to determine whether exercise-induced changes in metabolic responses observed in lowlanders staying at high altitude were related to acute or chronic increases in β-adrenergic stimulation. Our approach was to compare the metabolic responses to exercise in β-adrenergic blocked and non-blocked lowland residents at different times during a 20-day stay at high altitude (Pikes Peak). Propranolol, a widely prescribed drug which binds to β_1 and β_2 adrenoreceptor subtypes, or a matching placebo was administered to subjects during the first 15 days of residence at altitude, and then withdrawn to allow the drug to be cleared prior to the last day at high

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altitude. The effects of propranolol on metabolic responses occurring during exercise at high altitude have not been previously investigated.

Methods

Subjects and experimental design. Twelve healthy men ranging in age from 19 to 23 years volunteered as subjects for this study after being informed of the risks and requirements of participation. The subjects were receiving no regular medication. All were lifelong lowland residents who had not stayed at high altitude for at least 6 months prior to the investigation. Mean height and body mass (SE) of the subjects were 1.76 (0.003) m and 76 (3) kg, respectively. The subjects were divided into two groups, approximately matched for maximal oxygen uptake ($\dot{V}O_{2max}$). The groups were then randomly designated as the control [$\dot{V}O_{2max}$=48.6 (2.3) ml·kg^{-1}·min^{-1}], and experimental group [$\dot{V}O_{2max}$=48.9 (2.2) ml·kg^{-1}·min^{-1}].

At sea level (Natick, Mass.; 50 m), subjects completed $\dot{V}O_{2max}$ testing followed 1 day later by a 30-min submaximal exercise test. Both tests were completed a second time at sea level, 12 days following the first trials. No medication was given during the sea-level tests. Following the second test, the subjects commenced a medication program (propranolol or placebo) which continued for 3 days at sea level, at which point they were rapidly (within less than 8 h) transported to Pikes Peak, Colo. (4300 m). The medication regimen was continued uninterrupted until day 15 of residence at high altitude. The medication regimen for the experimental group consisted of 80 mg three times daily of oral propranolol (Ayerst Laboratories, New York, NY) for a total dose of 240 mg·day^{-1}. The control group received a matching placebo (lactose). The subjects were not informed who was receiving propranolol and who was received placebo.

The $\dot{V}O_{2max}$ tests were repeated on days 2 and 7 of residence at high altitude and the submaximal tests were repeated on days 3 and 8. Three days (16, 17, and 18) following discontinuation of medication were allowed for clearance of the drug. On day 19 of altitude residence, the $\dot{V}O_{2max}$ was again determined and on day 20 the subjects repeated the submaximal test. In addition, twice at sea level and on days 3, 8, 15 and 20 at high altitude, fasting blood samples were taken from the antecubital veins of subjects before they arose.

The submaximal tests consisted of 30 min of steady-state exercise. Exercise intensity was selected to elicit 80% of the $\dot{V}O_{2max}$ determined on the preceding day. To achieve the same relative exercise intensities, it was necessary to use lower power outputs at high altitude than were used at sea level; all submaximal tests at high altitude employed the same power output. Other investigators (Galbo et al. 1976) have studied catecholamine responses to exercise at sea level using a similar protocol, with subjects exercising at equivalent relative (i.e., % $\dot{V}O_{2max}$) rather than absolute exercise intensities in order to normalize for differences in $\dot{V}O_{2max}$ among subjects.

We have previously demonstrated that when exercise of the same % $\dot{V}O_{2max}$ is performed at sea level and high altitude, muscle glycogen utilization and plasma lactate accumulation are the same on arrival at altitude (unacclimatized) as at sea level, but decrease after acclimatization (Young et al. 1982b). Thus, our hypothesis would be supported if (a) lactate accumulation during exercise was the same during the 1st week at high altitude as at sea level in placebo-treated but reduced in propranolol-treated subjects; and (b) lactate accumulation during exercise was less on day 20 at high altitude than at sea level in placebo-treated, but the same as at sea level in propranolol-treated subjects.

Experimental procedures. All exercise was performed on a cycle ergometer (Monark, Varberg, Sweden) at a pedalling rate of 60 rev·min^{-1}. During exercise, heart rate, $\dot{V}O_2$, carbon dioxide output and minute ventilation were determined at 30-s ($\dot{V}O_{2max}$ tests) or 60-s (submaximal tests) intervals as described previously (Bender et al. 1989; Moore et al. 1986).

The procedure for determining $\dot{V}O_{2max}$ has been described in detail by Moore et al. (1986). For the submaximal tests, blood samples were obtained immediately before, 3 min after beginning and 3 min after completing 30 min of exercise. Blood samples were obtained from a catheter placed in an antecubital vein 30 min before exercise and kept patent by slow infusion 0.9% NaCl. Prior to and immediately at the completion of the submaximal exercise on the second trial at sea level and on day 20 of residence at 4300 m, vastus lateralis muscle samples were obtained by biopsy; the subjects were unmedicated on both of these occasions.

Blood samples were collected in ethylenediaminetetraacetic acid and an aliquot was assayed for lactate concentration within 15 min. The remaining blood was separated, and the plasma stored frozen in liquid nitrogen until analysis in triplicate for free fatty acid (Mizuno et al. 1980), glycerol (Bucolo and David 1973), glucose (Beckman automated analyzer, Beckman, Fullerton, Calif.), insulin (Serono Diagnostics radioimmunoassay kit, Serono Laboratory, Randolf, Mass.), norepinephrine and epinephrine (Davis et al. 1981) concentrations. Muscle samples for lactate analysis were frozen within several seconds of the biopsy by plunging the entire needle into liquid nitrogen. The post-exercise muscle sample for lactate analysis was frozen 5–10 s after exercise stopped. Muscle tissue for determination of glycogen concentration was obtained from a second "pass" through the same incision. The samples were divided into several pieces, cleaned of blood and connective tissue and stored in liquid nitrogen for subsequent analysis. Muscle samples were freeze-dried and enzymatic-fluorometric techniques were used to determine lactate (Diamant et al. 1968) and glycogen (Passonneau and Lauderdale 1974) concentrations.

Data analysis and statistical procedures. The data were analyzed using multifactor analysis of variance (ANOVA) for repeated measures. When factor main effects or multifactor interactions were found to be statistically significant ($P<0.05$) overall, Neuman-Keuls multiple-range critical difference was used to identify significant differences between means. All data are reported as the mean (SE). There were no significant differences between the two sea-level trials for any parameter; therefore data from the second trial were used to depict sea-level responses in the figures and tables.

Occasionally, missing metabolite values (e.g., insufficient sample or technical difficulties) had to be estimated to allow the ANOVA to be completed. In the case of missing pre-exercise resting values, the metabolite concentration measured in the fasting sample obtained that same morning was used. Other values were estimated using the procedure described by Snedecor and Cochran (1976). One control subject did not perform the exercise bouts on days 3 and 8 at high altitude due to an injury. Therefore, his data were not included in the ANOVA of the plasma metabolite data. He did complete the tests in which biopsies were performed; therefore his data were included in ANOVA of muscle glycogen and muscle lactate data.

Results

Cardiorespiratory responses to submaximal exercise

Cardiorespiratory data collected during the maximal and submaximal exercise bouts have been considered in detail elsewhere (Moore et al. 1986). Heart rate, power output, $\dot{V}O_2$, and % $\dot{V}O_{2max}$ during the final 5 min of the submaximal exercise tests are shown in Table 1. Consistent with effective β-adrenergic blockade, the heart rates of the experimental subjects were lower

Table 1. Exercise intensities and cardiorespiratory responses during the final 5 min of the submaximal exercise tests

	Control subjects				Experimental subjects			
	Sea level	Pike's Peak			Sea level	Pike's Peak		
		Day 3	Day 8	Day 20		Day 3	Day 8	Day 20
Power output (W)	186 (9)	141 (11)	141 (11)	133 (9)	206 (13)	142 (11)	142 (11)	145 (9)
$\dot{V}O_2$ ($ml \cdot min^{-1}$)	2740 (127)	2221 (178)	2202 (186)	1998 (124)	2984 (136)	2023 (141)	2290 (138)	2207 (91)
$\%\dot{V}O_{2max}$	79 (3)	88 (3)	87 (3)	79 (2)	80 (3)	80* (2)	91 (2)	84 (2)
Heart rate ($beats \cdot min^{-1}$)	179 (5)	175 (3)	171 (3)	164 (4)	175 (2)	122* (6)	122* (6)	166 (2)

Values are mean (SE)
* Varies significantly ($P<0.05$) from control subjects; $\dot{V}O_{2max}$, maximal oxygen consumption; $\dot{V}O_2$, oxygen consumption

($P<0.05$) than those of the control subjects during propranolol treatment. At sea level, there were no significant differences between the groups in power output, $\dot{V}O_2$ or $\%\dot{V}O_{2max}$ during exercise. There were no significant differences in relative exercise intensity between the sea-level and high-altitude tests. There were no significant differences in relative intensity between groups except on day 3 at high altitude when the $\%\dot{V}O_{2max}$ of the experimental subjects was slightly higher than in control subjects. As previously reported (Moore et al. 1986), differences in $\%\dot{V}O_{2max}$ between the groups were not observed at the 5th min of exercise.

At sea level, one subject from the experimental group became exhausted after 18 min of exercise, but all remaining subjects completed 30 min of exercise. On day 3 at high altitude, two control and one experimental subject stopped exercise after 10 min, and two other experimental subjects stopped after 15 and 20 min, respectively; the remaining men completed 30 min. All the experimental subjects and three control subjects completed the entire 30-min exercise bout on day 8 at 4300 m but two control subjects were still unable to continue exercising beyond the 10th min. All subjects completed 30 min of exercise on day 20 at 4300 m.

Basal catecholamine levels

Figure 1 shows the basal levels of circulating catecholamines measured at sea level and during the 20-day stay at high altitude. No significant differences were found in norepinephrine levels from control and experimental subjects so the data were pooled for the figure. There were no significant differences between the two sea-level norepinephrine measurements. Basal plasma norepinephrine concentrations were 1.96 (0.18) $nmol \cdot l^{-1}$ at sea level, and were unchanged on day 3 of residence at high altitude. By day 8 at high altitude, basal norepinephrine levels had increased significantly, and there was a further increase apparent on day 15 when norepinephrine levels reached 3.66 (0.32) $nmol \cdot l^{-1}$. Between days 15–20 of altitude residence, norepinephrine levels decreased significantly to 2.78 (0.30) $nmol \cdot l^{-1}$, but were still significantly higher than at sea level.

Basal epinephrine levels in the experimental group were not significantly different from those in the control group, so the data were pooled for Fig. 1. Basal

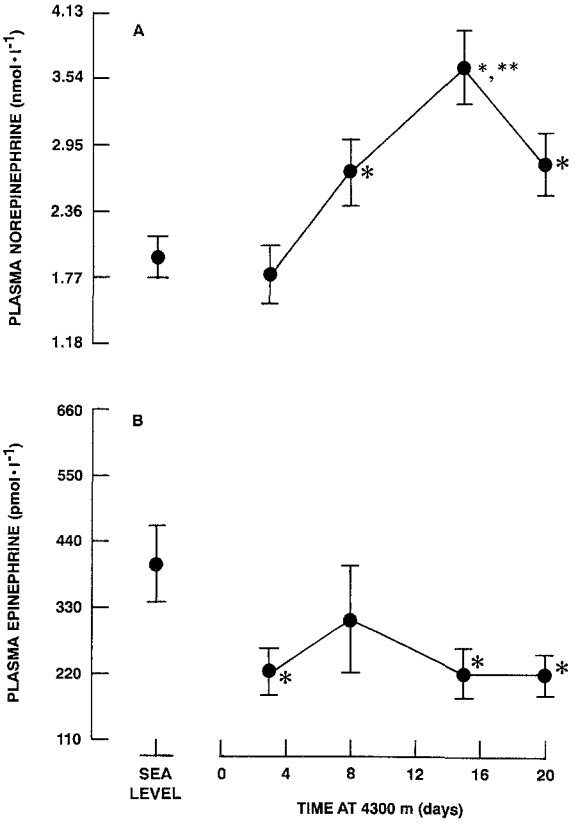

Fig. 1. Basal (i.e., fasting prior to arising in the morning) levels of circulating norepinephrine (**A**) and epinephrine (**B**) at sea level and during a 20 day stay on Pike's Peak. Values represent means (SE) from 12 subjects (data from placebo- and propranolol-treated subjects are pooled); * significantly different from sea level; *,** significantly different from days 8 and 20 at high altitude

Table 2. Plasma norepinephrine (nmol·l^{-1}) and epinephrine (pmol·l^{-1}) concentrations before and after 3 and 30 min of submaximal exercise at sea level and high altitude (4300 m)

		Control subjects				Experimental subjects			
		Sea level	Pikes Peak			Sea level	Pikes Peak		
	min		Day 3	Day 8	Day 20		Day 3	Day 8	Day 20
NE	0	1.66 (0.14)	2.69 (0.27)	4.85* (0.28)	4.75* (1.16)	1.60 (0.20)	3.04 (0.48)	5.56* (1.10)	4.30* (0.40)
	3	6.75** (1.44)	7.48** (0.58)	10.73*,** (1.53)	10.13*,** (1.41)	6.68** (0.39)	10.56** (1.48)	13.93*,** (0.98)	11.88*,** (1.15)
	30	9.85** (0.81)	11.87** (2.85)	12.18*,** (1.12)	10.83*,** (1.07)	6.65** (0.55)	5.43** (0.63)	13.12*,** (2.37)	10.43*,** (1.44)
E	0	380 (130)	400 (120)	280 (20)	260 (40)	270 (60)	200 (60)	220 (50)	240 (30)
	3	750 (150)	460 (90)	360 (70)	650 (120)	750 (130)	520 (110)	540 (130)	600 (50)
	30	1280 (170)	2900*,**,*** (1330)	640 (90)	710 (90)	1850 (930)	630 (170)	1690 (450)	950 (160)

Values are mean (SE) of norepinephrine (NE) and epinephrine (E) concentrations in control (placebo-treated, $n=5$) and experimental (propranolol-treated, $n=6$) subjects

* Significantly ($P<0.05$) different from sea level; ** significantly different from resting (0 min); *** significantly different from experimental subjects

plasma epinephrine concentrations decreased from 400 (70) pmol·l^{-1} at sea level to 220 (40), 220 (40) and 220 (60) pmol·l^{-1}, respectively, on days 3, 15 and 20 at 4300 m. There were no significant differences among basal epinephrine levels measured at high altitude.

Catecholamine response to exercise

Plasma catecholamine concentrations during rest and after 3 and 30 min of exercise are shown in Table 2. There were no significant differences in plasma norepinephrine levels between the control and experimental subjects. Plasma norepinephrine levels were increased ($P<0.02$) after 3 min of exercise, and there was no additional increment in norepinephrine level apparent after 30 min of exercise. On days 8 and 20 of residence at high altitude, norepinephrine levels (resting, post-exercise, following recovery) were higher ($P<0.01$) than at sea level.

Epinephrine levels increased with exercise, but this effect differed between sea level and high altitude, and between groups (i.e., a three-way interaction among factors). The only specific differences between means to achieve statistical significance involved comparisons with epinephrine concentrations of the control subjects after 30 min of exercise on day 3 at high altitude, which was higher than all other values.

Plasma lactate responses to exercise

The plasma lactate concentrations during the four submaximal exercise tests are shown in Fig. 2. Overall, lactate concentrations increased with exercise ($P<0.001$) and decreased with altitude exposure ($P<0.001$), but the magnitude of these effects varied with the duration

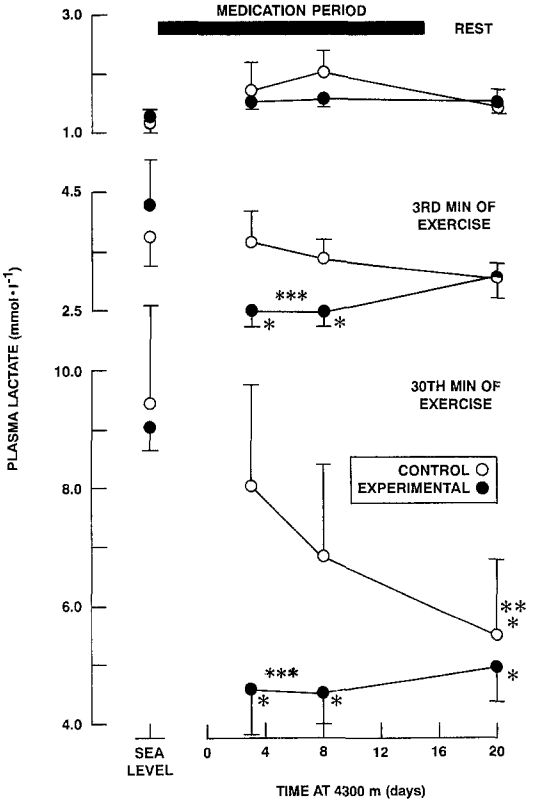

Fig. 2. Plasma lactate at rest (*top*) and following 3 (*middle*) and 30 min (*bottom*) exercise (80% $\dot{V}O_{2max}$) at sea level and on days 3, 8 and 20 of residence on Pike's Peak. Values represent means (SE) from control (*open circles*, $n=5$, placebo-treated) and experimental (*closed circles*, $n=6$, propranolol-treated) subjects. * Significantly different from sea level; ** significantly different from day 3 at high altitude; *** significantly different from control subjects. Sea-level data depicted are from unmedicated subjects; medication regimen was initiated 2 days before subjects ascended from sea level to 4300 m

of altitude exposure ($P<0.001$) and differed between the two groups ($P<0.03$). Resting plasma lactate concentrations (top panel, Fig. 2) did not differ significantly between control and experimental subjects and were not affected by high altitude.

In the control subjects, there were no significant differences in plasma lactate concentrations following 3 min of exercise (middle panel, Fig. 2) at sea level and any of the high altitude trials or among the three high-altitude trials. Lactate levels at the completion of 30 min exercise (bottom panel, Fig. 2) tended to decrease with time at 4300 m, and the difference in levels at sea level and high altitude achieved statistical significance on day 20 at 4300 m.

Plasma lactate concentrations tended to be lower in the experimental than control subjects throughout the propranolol treatment period at high altitude but differences between groups were statistically significant only on day 3 at 4300 m; there were no differences between the groups at sea level. In the experimental subjects, plasma lactate concentrations after 3 min of exercise were lower on days 3 and 8 at 4300 m (when propranolol was being taken) than at sea level, but on day 20 at 4300 m (5 days after withdrawal of propranolol), values were not significantly different from sea level values. In the experimental subjects, plasma lactate concentrations after 30 min of exercise were less on days 3, 8 and 20 at 4300 m than at sea level.

Other plasma metabolite responses to exercise

Plasma free fatty acid and glycerol concentrations for control and experimental subjects did not differ significantly; therefore the data for the two groups were combined and are shown in Table 3. Resting free fatty acid levels fell during the 1st week of residence at 4300 m, and the difference became statistically significant by day 8 at altitude. Resting free fatty acid levels then rose, becoming significantly higher than sea level values on day 20 at altitude. At sea level, exercise resulted in an increase in free fatty acid levels which was statistically significant after 30 but not 3 min of exercise. On days 3 and 8 at 4300 m, free fatty acid concentrations during exercise did not differ from resting levels, and were lower than levels during exercise at sea level. On day 20 at 4300 m, free fatty acid levels were significantly increased above resting levels after 3 min of exercise and there was a further increase apparent after 30 min of exercise. Free fatty acid concentrations during exercise were higher on day 20 at altitude than on days 3 or 8, or at sea level. Exercise resulted in an increase in glycerol concentrations when compared to resting levels. Glycerol concentrations during rest or exercise were not significantly affected by altitude exposure.

Plasma glucose and insulin concentrations did not differ significantly between control and experimental subjects. Altitude exposure had no significant effect on plasma glucose concentrations; however, the levels rose significantly from resting levels after 30 min exercise [5.0 (0.2) vs 5.8 $mmol \cdot l^{-1}$]. Insulin concentrations during rest on day 8 of residence at 4300 m [405 (93) $pmol \cdot l^{-1}$] were significantly higher than resting levels at sea level [196 (56) $pmol \cdot l^{-1}$] or on days 3 [139 (22) $pmol \cdot l^{-1}$] and 20 [161 (68) $pmol \cdot l^{-1}$] at altitude. At sea level, insulin concentrations fell significantly during the first 3 min of exercise [55 (6) $pmol \cdot l^{-1}$], but returned to resting levels after 30 min. On days 3 and 20 of residence at 4300 m, insulin concentrations remained unchanged from resting levels with exercise. On day 8 at altitude, insulin concentrations fell below resting levels after 3 min [158 (27) $pmol \cdot l^{-1}$] of exercise and remained significantly reduced after 30 min [197 (52) $pmol \cdot l^{-1}$].

Table 3. Plasma free fatty acid ($mg \cdot l^{-1}$) and glycerol ($mmol \cdot l^{-1}$) concentrations before and after 3 and 30 min of submaximal exercise at sea level and high altitude (4300 m)

		Sea level	Pike's Peak		
	min		Day 3	Day 8	Day 20
Free fatty acids	0	100 (20)	60 (10)	50* (10)	120* (20)
	3	90 (10)	50* (10)	40* (10)	150*,** (30)
	30	180** (30)	90* (20)	60* (10)	230*,** (40)
Glycerol	0	0.06 (0.01)	0.08 (0.01)	0.13 (0.04)	0.09 (0.01)
	3	0.10 (0.01)	0.13 (0.02)	0.14 (0.04)	0.13 (0.02)
	30	0.22** (0.03)	0.15** (0.02)	0.20** (0.03)	0.24** (0.01)

Values are mean (SE); $n=11$
* Significantly ($P<0.05$) different from sea level; ** significantly different from resting (0 min)

Skeletal muscle metabolite responses to exercise

Muscle glycogen concentration for both control and experimental groups before and after submaximal exercise bouts at sea level and at high altitude on day 20 are shown in Table 4. Glycogen utilization (calculated for each individual as pre- minus post-exercise muscle glycogen concentration) did not differ significantly between control and experimental subjects during exercise at sea level or on day 20 at high altitude, but was less ($P<0.02$) during exercise on day at 4300 m compared to sea level. There were no significant differences between control and experimental subjects in muscle lactate concentrations at rest or following exercise. Muscle lactate increased ($P<0.01$) with exercise at both sea level and high altitude on day 20. There appeared to be a tendency ($P<0.09$) for muscle lactate to be lower following exercise at altitude [1.5 (0.7) $mmol \cdot kg$ dry $tissue^{-1}$] as compared to sea level [2.7 (0.7) $mmol \cdot kg$ dry $tissue^{-1}$]. However, muscle lactate accumulation (pre-minus post-exercise muscle lactate concentration) did not differ significantly for sea level and high altitude.

Table 4. Utilization of muscle glycogen (mmol glucose·kg^{-1} dry tissue) during 30 min of submaximal exercise at sea level and high altitude (4300 m)

	Control subjects		Experimental subjects	
	Sea level	Pike's Peak Day 20	Sea level	Pike's Peak Day 20
Pre-ex	403	397	409	324
	(49)	(34)	(31)	(30)
Post-ex	205	253	236	229
	(22)	(34)	(29)	(25)
Utilization	198	144*	174	95*
	(37)	(42)	(17)	(28)

Values are means (SE) of muscle glycogen concentration before (Pre-ex) and after (Post-ex) exercise;
* Significantly different from sea level

Discussion

We investigated the hypothesis that the effects of high-altitude exposure on blood lactate response to exercise in unacclimatized lowlanders, and the subsequent adaptation of this response during acclimatization resulted from acute and chronic increases in β-adrenergic stimulation. The main finding of this study, that plasma lactate concentration during exercise on day 3 at high altitude increased to the same levels observed in placebo-treated but not propranolol-treated subjects at sea level, supports the hypothesis.

Our data suggest that epinephrine release during exercise is determined more by the $\% \dot{V}O_{2max}$ than absolute exercise intensity. Plasma epinephrine concentrations during exercise on day 3 at high altitude increased to the same level or higher in propranolol- or placebo-treated subjects than at sea level, despite the reduction in absolute power output necessary to maintain the relative exercise intensity constant. Sea-level investigations support this concept. Wolfel et al. (1990) reported that at a given absolute exercise intensity, plasma epinephrine concentrations were reduced in subjects who had completed a physical training program which increased $\dot{V}O_{2max}$ and thus reduced the relative intensity for a given absolute intensity.

Although acute high-altitude exposure affected circulating epinephrine concentrations similarly in both propranolol- and placebo-treated subjects, the altitude effect on lactate responses to exercise differed between groups. Plasma lactate concentrations in the unacclimatized control subjects increased to the same level during exercise on day 3 at high altitude as at sea level. These findings are consistent with our previous findings (Young et al. 1982a, b) and those of others (Hermansen and Saltin 1967; Knuttgen and Saltin 1973; Maher et al. 1974). In subjects receiving propranolol, plasma epinephrine concentrations increased to the same level during exercise on day 3 at high altitude as at sea level, but plasma lactate concentrations were substantially lower than at sea level. The constant level of β-adrenergic stimulation during exercise of the same relative intensity performed under conditions of normoxia and acute hypoxia appears to be responsible for the equivalent plasma lactate response observed in non-adrenergic-blocked subjects in this and previous investigations.

It has often been suggested that reduced arterial oxygen content at high altitude limits oxygen availability to the muscle during exercise and that this results in increased lactate accumulation. However, Bender et al. (1989) demonstrated that for a given absolute exercise intensity, increased muscle blood flow offsets the reduced arterial oxygen content; thus oxygen delivery to the exercising leg is the same under acute hypoxic conditions as for normoxia. Nevertheless, net lactate release by the muscle increases. A given absolute exercise intensity corresponds to a higher relative exercise intensity at high altitude than at sea level, since $\dot{V}O_{2max}$ decreases at altitude. Our data suggest that lactate release increases during exercise at a given absolute intensity with acute hypoxia as compared to normoxia because the increase in relative intensity results in greater epinephrine release and β-adrenergic stimulation.

That β-adrenergic blockade prevented blood lactate concentrations from rising as high during exercise on day 3 at high altitude as at sea level is consistent with the results of sea-level studies (Chasiotis et al. 1983; Kaiser et al. 1985). Chasiotis et al. (1983) reported that propranolol treatment reduced lactate accumulation by decreasing muscle glycogen breakdown during exercise. On the other hand, Kaiser et al. (1985) observed that propranolol treatment reduced blood lactate accumulation during exercise but muscle glycogen breakdown was unaffected. Whether or not propranolol inhibited glycogenolysis in the present study cannot be determined since muscle biopsies were not performed in conjunction with the exercise tests during the medication period.

Our findings do not support the hypothesis that chronically increased β-adrenergic stimulation is responsible for the reduction in lactate accumulation which occurs during exercise during altitude acclimatization. For our hypothesis to be supported, β-adrenergic blockade should have prevented this adaptation from taking place during altitude acclimatization. However, we found that both placebo-treated subjects and those treated with propranolol for the first 15 days of altitude acclimatization experienced a smaller increment in blood lactate concentration and utilized less muscle glycogen during the exercise bout on day 20 at 4300 m than at sea level.

The changes in circulating catecholamine concentrations observed as the subjects in this study acclimatized to high altitude indicate a progressive increase in β-adrenergic stimulation due to sympathetic nervous activity. One possible explanation for the failure of propranolol treatment to prevent the changes in lactate accumulation during acclimatization is that adequate β-blockade was not maintained. This might have been the case if propranolol had potentiated the sympathetic

nervous response to high altitude. However, propranolol had no effect on plasma norepinephrine concentrations at rest or following exercise at high altitude. This finding is in agreement with observations made on seated subjects at sea level (Irving et al. 1974), although propranolol has been observed to increase the resting norepinephrine concentration in standing subjects, probably as a result of greater baroreceptor activity (Galbo et al. 1976). An affect of altitude acclimatization and/or propranolol on beta-adrenergic receptor density cannot be ruled out (Voelkel et al. 1981).

Plasma norepinephrine levels (basal and during exercise) were increased at high altitude as compared with values at sea level. These effects were not apparent during the first few days at 4300 m but required several days of acclimatization to develop. Our observation that basal norepinephrine levels peaked between days 8 and 15 at high altitude and began to decline thereafter has not previously been reported. Thus, the increased sympathetic nervous activity experienced by lowlanders staying at high altitude is a transient response to altitude exposure.

This is the first study in which basal levels of circulating epinephrine have been found to be decreased during a stay at high altitude. The method of catecholamine analysis used in earlier studies (Cunningham et al. 1965) may not have been sensitive enough to detect this change. Although the physiological significance of a reduction in adrenal medullary activity during altitude acclimatization is unclear, it may be a compensatory response to the increased sympathetic activity.

We have confirmed our previous observation (Young et al. 1982b) that the glycogen sparing effect of altitude acclimatization is associated with changes in plasma free fatty acids during exercise. Plasma free fatty acid concentrations rose to higher levels during exercise on day 20 than at sea level or on days 3 or 8 at high altitude. Greater mobilization and availability of free fatty acids could enable a reduction in glycogen utilization and lactate accumulation. However, Sutton et al. (1983) have questioned whether a shift to fat metabolism is a direct effect of altitude acclimatization per se, or rather the secondary effect of the low carbohydrate/hypocaloric diet often assumed by altitude sojourners. The lack of a significant difference between pre-exercise glycogen levels at sea level and high altitude suggests that carbohydrate consumption was adequate in these subjects, but we did not control or monitor diet. Further investigation of the regulation of exercise metabolism at high altitude requires a study in which diet is carefully controlled.

This study has demonstrated several new findings. Firstly, the effects of acute hypoxia on lactate accumulation in unacclimatized lowlanders exercising at high altitude appear to be mediated by circulating epinephrine acting on β-adrenergic receptors. Secondly, chronic stimulation of β-adrenergic receptors by elevated levels of circulating norepinephrine is not the mechanism responsible for the changes in lactate accumulation that occur during exercise during altitude acclimatization. And thirdly, the increase in sympathetic nervous activity during a prolonged stay at high altitude appears to be a transient response, peaking between the 1st and 2nd week of residence at high altitude, and then declining.

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