Acclimatization to high altitude increases muscle sympathetic activity both at rest and during exercise

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Mazzeo, Robert S., George A. Brooks, Gail E. Butterfield, Deborah A. Podolin, Eugene E. Wolfel, and John T. Reeves. Acclimatization to high altitude increases muscle sympathetic activity both at rest and during exercise. *Am. J. Physiol.* 269 (*Regulatory Integrative Comp. Physiol.* 38): R201–R207, 1995.—This investigation examined the relationship between alterations in plasma norepinephrine associated with 21 days of high-altitude exposure and muscle sympathetic activity both at rest and during exercise. Healthy sea level residents, divided into a control group (n = 5) receiving a placebo or a drug group (n = 6) receiving 240 mg/day of propranolol, were studied while at sea level, upon arrival (acute), and after 21 days of residence (chronic) at 4,300 m. Arterial norepinephrine levels and net leg uptake and release of norepinephrine were determine both at rest and during 45 min of submaximal exercise via samples collected from femoral arterial and venous catheters. Arterial norepinephrine levels increased significantly after chronic altitude exposure both at rest (84%) and during exercise (174%) compared with sea level and acute values. A net uptake of norepinephrine was found in resting legs at sea level (0.28 ± 0.05 nmol/min) and with acute exposure (0.07 ± 0.06 nmol/min); however, a significant switch to net leg norepinephrine release was observed with chronic altitude exposure (0.51 ± 0.11 nmol/min). With exercise, a net release of norepinephrine by the leg occurred across all conditions with chronic exposure, again eliciting the greatest values (5.3 ± 0.6, 8.0 ± 1.7, and 14.4 ± 3.1 nmol/min for sea level, acute, and chronic exposure, respectively). It was concluded that muscle sympathetic activity is significantly elevated both at rest and during submaximal exercise as a result of chronic high-altitude exposure, and muscle is a major contributor to the increase in plasma norepinephrine levels associated with prolonged altitude exposure. The presence of dense β-blockade did not alter this adaptation to altitude.

norepinephrine; epinephrine; uptake; release

WE HAVE PREVIOUSLY documented the sympathoadrenal responses associated with both acute and chronic exposure to high altitude (13, 15, 18). Specifically, we have demonstrated that on acute exposure (within 4 h of arrival), arterial concentrations of epinephrine are significantly elevated both at rest and during submaximal exercise compared with sea level values. After 3 wk of acclimatization, arterial epinephrine levels declined toward sea level values. However, the norepinephrine response, as measured by both arterial and urinary levels, reacted in a very different manner from that observed for epinephrine. Norepinephrine levels during acute exposure were similar to those found at sea level; however, concentrations rose significantly with time during the 21-day acclimatization period.

Measurement of blood and urinary catecholamine levels, however, does not reveal much information regarding their source or origins. The major source of circulating epinephrine is from adrenal release, whereas norepinephrine levels primarily represent spillover of the neurotransmitter from sympathetic nerve endings (7, 8). Since muscle comprises a large percentage of the body mass, an increase in sympathetic activity from this vascular bed would make a significant contribution to the arterial and urinary excretion of norepinephrine demonstrated with prolonged altitude exposure. Direct measurement of muscle sympathetic nerve activity, with the use of microneurography, does indicate that sympathetic activity is significantly elevated in humans during an acute hypoxic stimulus (12, 20, 21); however, to date no studies have examined the effect of chronic hypoxia on muscle sympathetic activity. Studies in rats subjected to chronic hypoxic conditions (14 days) have demonstrated an increase in sympathetic activity and norepinephrine turnover measured directly in cardiac muscle (10). Unfortunately, no measurements were made in skeletal muscle.

In response to a single bout of exercise performed at sea level, it has been demonstrated in both humans (22, 23) and dogs (17) that active skeletal muscle was the major source of norepinephrine released into the circulation. However, again no studies exist examining the contribution of exercising skeletal muscle to the norepinephrine released into plasma during either acute or chronic hypoxia.

Thus it was hypothesized that during chronic exposure to high altitude skeletal muscle sympathetic activity would be significantly elevated compared with sea level, thereby contributing to the elevations in arterial and urinary norepinephrine content previously reported. It was a purpose of this investigation to examine muscle sympathetic activity, as determined by net norepinephrine release in the leg, both at rest and during 45 min of submaximal exercise at sea level, during acute exposure, and after 3-wk acclimatization to high altitude (4,300 m).

METHODS

Eleven male subjects who resided at sea level (age = 26.7 ± 1.2 yr; weight = 71.4 ± 3.2 kg) participated in the study Subjects were nonsmoking individuals not involved in regular endurance training. All subjects signed an informed consent form approved by the Human Subjects Committee of the

University of Colorado-Health Sciences Center, the Palo Alto Veterans Affairs Hospital, the University of California, Berkeley, and United States Army Research Institute of Environmental Medicine. Subjects were randomly assigned either to a control group (n = 5) receiving a placebo or to a β-blocked group (n = 6) receiving propranolol at 240 mg/day. This dosage has been shown to be effective in inducing dense β-blockade in subjects both at sea level and during altitude exposure (14). The degree of β-blockade was documented in our subjects by monitoring heart rate response to intravenously infused isoproterenol (14). Administration of placebo or drug began 3 days before sea level and altitude testing and continued throughout the 21 days at 4,300 m. β-Blockade was used because this study was part of a larger project designed to examine the effects of β-adrenergic blockade on metabolic and hemodynamic adjustments during high-altitude acclimatization. Altitude studies were performed 3 wk after sea level experiments. Sea level experiments were performed at the Palo Alto Veterans Affairs Medical Center, Palo Alto, CA (barometric pressure = 751 Torr). Altitude tests were performed within the first 4 h of arrival at 4,300 m (Pikes Peak, CO; 461–463 Torr) and after 21 days of residence at the summit of Pikes Peak. Subject arrival at altitude was staggered. Subjects traveled by air from sea level to Denver, CO, and slept at 1,954 m (Manitou Springs, CO) the night before ascending by car to 4,300 m. Caloric intake as well as physical activity were regulated across all experimental conditions to avoid weight and exercise fluctuations as previously described (3).

Exercise protocol. Maximal oxygen consumption ($\dot{V}O_{2max}$) was determined from a continuous progressive exercise test on an electrically braked bicycle ergometer with 25-W increments each 2 min. Tests of $\dot{V}O_{2max}$ were performed at sea level and on *days 4*, and *19* at altitude. $\dot{V}O_2$, CO_2 production ($\dot{V}CO_2$), and minute ventilation ($\dot{V}_E$) were determined using standard on-line open-circuit techniques (AMETEK S-3A oxygen and Beckman LB-2 carbon dioxide analyzers, Validyne MP 45 pressure transducer, and Fleisch no. 3 pneumotachometer).

Submaximal exercise tests were performed at sea level within 4 h of arrival to high altitude (acute) and after 21 days of residence at high altitude (chronic). Before exercise, subjects rested quietly for at least 90 min seated in a chair. Subjects then performed submaximal steady-state exercise on the bicycle ergometer for 45 min at an intensity that elicited 50% $\dot{V}O_{2max}$ obtained at sea level. During acute and chronic altitude exposure, an absolute exercise intensity similar to that of sea level was chosen so that subjects were working at the same absolute $\dot{V}O_2$ across all three conditions (14). Respiratory measurements and blood samples were collected at rest (−15 and 0 min before exercise) and at 5, 15, 30, and 45 min of exercise.

Blood analyses. The femoral artery and vein were cannulated using standard percutaneous techniques (25). Arterial and venous blood samples were collected simultaneously in heparinized tubes containing reduced glutathione (to control catechol oxidation) for subsequent catecholamine determinations by means of high-performance liquid chromatography (HPLC) with electrochemical detection. An internal standard was prepared by adding appropriate levels of dihydroxybenzlamine (Sigma) in 50 μl of 0.1 N perchloric acid (PCA) to the plasma. The pH of the solution was adjusted to >8 with 1.5 M tris(hydroxymethyl)aminomethane buffer at pH 8.6 in 2% EDTA. Twenty-five milligrams of acid-washed alumina (Woelm, ICN Pharmaceuticals) were added followed by 10 min of vigorous shaking. The alumina was then washed three times with 3 ml of distilled water with brief centrifugation between washes. The catecholamines were extracted with 100 μl of 0.1 N PCA with 10 min of shaking and final centrifugation at 12,000 *g*. Overall recoveries averaged >80%. One hundred microliters of sample eluant were injected into the HPLC column (reverse phase, Bio-Sil ODS-5S, Bio Rad) and eluted with mobile phase (6.8 g sodium acetate-anhydrous, 1.0 g sodium heptane sulfonate, 60 ml acetonitrile, 1.0 g Na_2EDTA in 1 liter adjusted to a pH of 4.8). The flow rate was 1.1 ml/min at 2,000 lb/in.^{2} with a potential of 0.65 V. The chromatogram was analyzed by computer integration (model C-R3A, Shimadzu).

Arterial and venous leg P_{O_2}, as well as oxygen content, were measured independently for each blood sample (OSM 3 Hemoximeter, Radiometer, Copenhagen) both at rest and during exercise. Leg $\dot{V}O_2$ was then determined as previously described (25).

Net uptake/release of catecholamines across the leg (both at rest and during exercise) was calculated as [arterial − venous (a-v)] catecholamine difference times leg blood flow times 2 legs. Leg blood flow was determined as previously described (25). Briefly, a 10-ml bolus of sterile saline (0°C) was infused via the venous catheter, and flow was measured in triplicate by thermodilution with a cardiac computer (American Edwards Laboratories model 9520). Thermodilution curves were validated on a Soltec recorder (model 8K22).

Statistics. Values reported are means ± SE. Differences across all testing conditions (sea level and altitude) were determined by a repeated measures analysis of variance with significance at $P < 0.05$. Tukey post hoc comparisons were used to identify significant differences among means.

RESULTS

Oxygen consumption. $\dot{V}O_{2max}$ decreased significantly on arrival to altitude compared with sea level values (44.7 ± 2.1 vs. 35.5 ± 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$ for sea level and acute altitude, respectively). There was no further change in $\dot{V}O_{2max}$ by *day 19* at altitude (36.5 ± 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$). Values for $\dot{V}O_{2max}$ did not differ between control and blocked subjects under any condition. During submaximal exercise, the work output was kept constant (87.8 ± 1.7 W), which yielded similar absolute $\dot{V}O_2$ values for sea level and both altitude conditions but resulted in a higher relative $\dot{V}O_2$ at altitude than at sea level (49, 67, and 66% $\dot{V}O_{2max}$ for sea level, acute, and chronic altitude, respectively) as we have reported previously (14). Values for $\dot{V}O_2$ remained stable throughout the 45 min of exercise. During exercise, $\dot{V}O_2$, when expressed in absolute or relative terms, did not differ between control and blocked subjects nor were any differences found in $\dot{V}O_2$ between acute and chronic altitude exposure.

Plasma catecholamines. Arterial catecholamine levels observed for all subjects both at rest and during the 45-min submaximal exercise bout are reported in Table 1. No differences in resting norepinephrine levels were found between sea level and acute altitude exposure for either control or blocked subjects. However, after 21 days residence at altitude, norepinephrine levels at rest were significantly elevated compared with sea level in all subjects (84 and 86% for control and blocked subjects, respectively). Norepinephrine levels were higher during exercise compared with rest across all subjects and conditions. Unlike resting values, norepinephrine levels during exercise were significantly greater after acute

Table 1. *Arterial norepinephrine and epinephrine levels at rest and during exercise at sea level and acute and chronic high-altitude exposure*

	Sea Level	Acute	Chronic
	Norepinephrine, nM		
Controls			
Rest	2.19 ± 0.35	1.77 ± 0.30	4.02 ± 0.35†
Exercise	6.21 ± 0.77	11.11 ± 2.01‡	17.02 ± 2.90†
β-Blocked			
Rest	1.71 ± 0.41	1.89 ± 0.24	3.19 ± 0.30†
Exercise	5.91 ± 0.47	9.46 ± 1.54*	12.29 ± 2.19*
	Epinephrine, nM		
Controls			
Rest	0.55 ± 0.11	1.42 ± 0.38‡	0.82 ± 0.22
Exercise	1.42 ± 0.27	3.22 ± 0.98‡	1.64 ± 0.27
β-Blocked			
Rest	0.27 ± 0.05	1.20 ± 0.16‡	0.82 ± 0.16†
Exercise	1.75 ± 0.38	4.04 ± 0.87‡	2.89 ± 0.44*

Values are means ± SE. *Significantly different from sea level; †significantly different from sea level and acute exposure ($P < 0.05$); ‡significantly different from sea level and chronic exposure.

altitude exposure compared with sea level (79 and 60% for control and blocked subjects, respectively). Norepinephrine levels increased even more after 21 days at altitude in response to exercise (174 and 108% for control and blocked subjects, respectively).

Plasma epinephrine values at rest increased with acute altitude exposure in both groups of subjects and returned to sea level values after chronic exposure in the control group but remained elevated in the β-blocked subjects (Table 1). Exercise resulted in epinephrine levels greater than those at rest, but the pattern was similar across altitude conditions. Thus acute altitude exposure elicited the greatest increase in exercising epinephrine values in both β-blocked (131%) and control (127%) subjects. After 21 days residence at 4,300 m, epinephrine values during exercise declined in comparison to acute altitude values and were similar to those at sea level for control subjects but did not reach sea level values for the β-blocked subjects.

Leg blood flow and oxygen content. Leg blood flow at rest did not differ across altitude conditions for either group but was significantly lower at all times for blocked subjects compared with controls (Table 2). During submaximal exercise, leg blood flow was significantly elevated compared with rest for all subjects across all

Table 2. *Leg blood flow at rest and during exercise at sea level and acute and chronic high-altitude exposure*

	Sea Level	Acute	Chronic
	Blood flow, ml/min		
Rest			
Control	773 ± 68	651 ± 50	764 ± 53
β-Blocked	532 ± 15*	547 ± 23*	559 ± 19*
Exercise			
Control	3,928 ± 242	3,838 ± 235	3,377 ± 359
β-Blocked	3,396 ± 123*	3,471 ± 97*	3,227 ± 129

Values are means ± SE. Blood flows are given for one leg only. *Significantly different from control group ($P < 0.05$).

Table 3. *Whole body and leg $\dot{V}O_2$ uptakes at rest and during 45 min of submaximal exercise*

	Sea Level	Acute	Chronic
	Whole body $\dot{V}O_2$, $ml \cdot kg^{-1} \cdot min^{-1}$		
Controls			
Rest	4.3 ± 0.5	4.9 ± 0.4	5.3 ± 0.3*
Exercise	21.3 ± 1.0	24.0 + 1.1	23.8 + 1.0
β-Blocked			
Rest	4.1 ± 0.2	4.2 ± 0.1	4.8 ± 0.2*
Exercise	21.9 ± 0.8	23.5 ± 0.7	23.5 ± 0.7
	Leg $\dot{V}O_2$, ml/min		
Control			
Rest	20.9 ± 2.4	22.3 ± 6.1	22.9 ± 4.4
Exercise	449.6 ± 21.5	445.6 ± 28.7	492.4 ± 55.5
β-Blocked			
Rest	32.3 ± 3.4	35.5 ± 7.0	30.4 ± 5.1
Exercise	499.9 ± 17.9	474.4 ± 20.1	519.5 ± 28.5

Values are means ± SE. Leg $\dot{V}O_2$ values are for one leg only. *Significantly different from sea level ($P < 0.05$).

conditions. Leg blood flow during exercise at altitude was not different from sea level values in either group. Flow during exercise was lower in the blocked group for sea level and acute altitude exposure compared with controls (Table 2).

Total body, as well as leg, $\dot{V}O_2$ did not differ during the 45-min submaximal exercise bout across any of the conditions studied (Table 3). Total body $\dot{V}O_2$ at rest, however, was significantly greater after 3-wk acclimatization compared with sea level or acute altitude exposure in both control and blocked groups.

Net uptake and release of catecholamines. From arteriovenous catecholamine differences (Table 4) and femoral blood flows, net uptake and release of norepinephrine and epinephrine by the leg were determined. At sea level, under resting conditions, a net uptake of norepinephrine by the legs was observed in both groups of subjects (Fig. 1). With acute altitude exposure, net uptake was reduced to modest levels; however, after

Table 4. *Arteriovenous difference for norepinephrine and epinephrine from resting and exercising legs at sea level and acute and chronic high-altitude exposure*

	Sea Level	Acute	Chronic
	Norepinephrine, nM		
Controls			
Rest	0.189 ± 0.053	0.059 ± 0.130	−0.331 ± 0.154†
Exercise	−0.680 ± 0.183	−1.040 ± 0.337	−2.140 ± 0.443†
β-Blocked			
Rest	0.402 ± 0.142	0.030 ± 0.083*	−0.449 ± 0.166†
Exercise	−0.532 ± 0.195	−0.774 ± 0.195	−1.998 ± 0.366†
	Epinephrine, nM		
Controls			
Rest	0.240 ± 0.027	0.873 ± 0.087*	0.399 ± 0.120†
Exercise	0.268 ± 0.071	0.595 ± 0.153*	0.202 ± 0.060
β-Blocked			
Rest	0.158 ± 0.060	0.824 ± 0.131*	0.448 ± 0.109†
Exercise	0.338 ± 0.098	0.491 ± 0.164	0.431 ± 0.147

Values are means ± SE. *Significantly different from sea level and chronic exposure; †significantly different from sea level and acute exposure ($P < 0.05$).

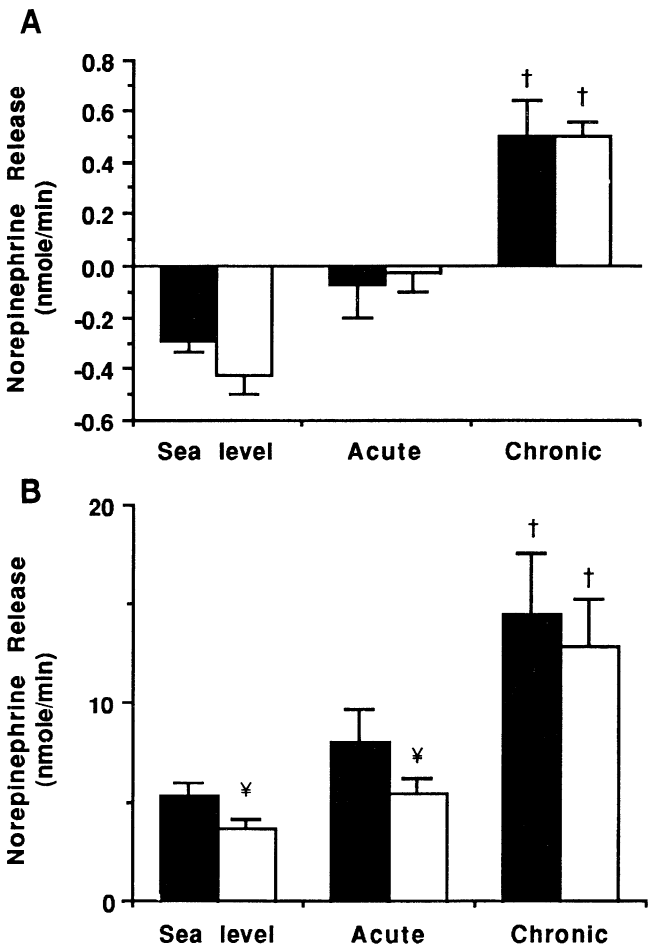

Fig. 1. Net norepinephrine release calculated for both legs while at rest (*A*) and during 45 min of submaximal exercise (*B*) across sea level, acute, and chronic high-altitude conditions [n = 5 and 6 for control (filled bars) and β-blocked (open bars) groups, respectively]. †Significantly different from both sea level and acute values; ¥ significantly different from the control group ($P < 0.05$).

chronic exposure, a dramatic shift to a significant net release of norepinephrine from resting legs was demonstrated. These changes occurred to a similar extent in both control and blocked subjects (Fig. 1). During 45 min of submaximal exercise, all subjects demonstrated a significant increase in release of norepinephrine from the legs compared with rest. Again, net release was greater for chronic altitude exposure compared with the other conditions in both groups of subjects. Additionally, during exercise net norepinephrine release was lower in the β-blocked subjects at sea level and with acute exposure compared with controls.

A net uptake of epinephrine by the legs was present both at rest and during exercise for all subjects across all conditions (Fig. 2). Epinephrine uptake was always significantly greater with acute altitude exposure compared with sea level (rest: 1.1 ± 0.2 vs. 0.4 ± 0.1 nmol/min for controls and 0.9 ± 0.2 vs. 0.2 ± 0.01 nmol/min for blocked; exercise: 4.6 ± 0.5 vs. 2.1 ± 0.5 nmol/min for controls, 3.4 ± 0.5 vs. 2.3 ± 0.5 nmol/min for blocked). After 21-days residence at 4,300 m, leg epinephrine uptake returned to values observed at sea level for both rest and exercise.

DISCUSSION

The major finding of the present investigation was that the resting legs made a dramatic switch from net norepinephrine uptake at sea level and during acute altitude exposure to a significant net release after 21 days chronic exposure to high altitude. This represents a quantitative rather than a qualitative change in outward norepinephrine release, since flux across muscle is bidirectional (7, 8). This elevation in sympathetic activity to the legs, associated with chronic altitude exposure, was also significantly greater during submaximal exercise compared with the other conditions.

Previous investigations have consistently demonstrated elevations in both plasma and urinary norepinephrine levels over time at high altitude (13, 15, 18). Although the mechanisms responsible for this observation remain uncertain, it is apparent from the present investigation that skeletal muscle makes a significant contribution to the alterations in plasma norepinephrine levels observed. Plasma levels of norepinephrine are a function of the rate of spillover into the circulation (~10–20% of the norepinephrine released by sympathetic nerves under resting conditions), a small amount

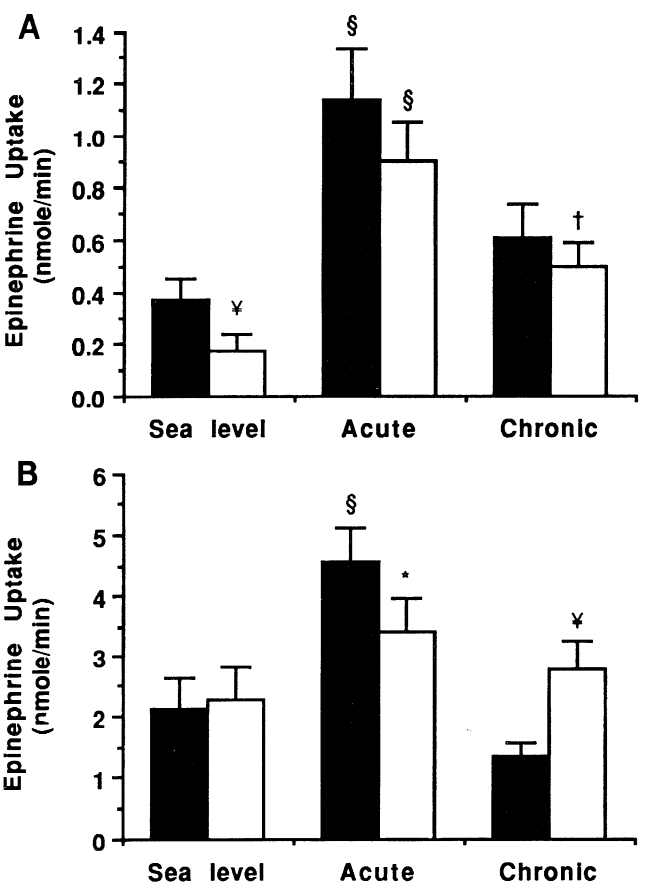

Fig. 2. Net epinephrine uptake for both legs while at rest (*A*) and during 45 min of submaximal exercise (*B*) across sea level, acute, and chronic high-altitude conditions [n = 5 and 6 for control (filled bars) and β-blocked (open bars) groups, respectively]. †Significantly different from both sea level and acute values; §significantly different from both sea level and chronic values; *significantly different from sea level values; ¥ significantly different from the control group ($P < 0.05$).

secreted by the adrenal medulla, and the rate of its removal or clearance from the plasma pool (7). There appear to be no direct effects of hypoxia on enhancing the prejunctional release of neuronal norepinephrine or on intraneuronal metabolism and uptake of the neurotransmitter in muscle (10, 19), suggesting that the enhanced spillover observed in the present study is directly related to an increase in sympathetic activity. Both no change and an increase in clearance of plasma norepinephrine have been reported during acute hypoxia (12, 20). An increase in clearance would actually tend to lower plasma levels and therefore would not explain the increases associated with altitude; however, no studies have examined the effect of chronic high-altitude exposure on plasma clearance of norepinephrine.

Regional blood flow is also a factor that can influence the rate of norepinephrine spillover, with greater flow rates enhancing the washout of norepinephrine (4, 5, 17). Because leg blood flow in the present investigation was not different across all altitude conditions (Table 2), it is unlikely that washout of norepinephrine from the muscle beds is responsible for the elevation in net norepinephrine release found with chronic altitude exposure. This would suggest that an increase in sympathetic activity to skeletal muscle is a major mechanism contributing to elevated plasma and urinary norepinephrine levels witnessed during chronic altitude exposure. Because a large percentage of our body mass is composed of muscle, an increase in sympathetic activity to these vascular beds, resulting from prolonged high-altitude exposure, would significantly impact on circulating norepinephrine content. Further support of this concept is found from direct measurements of sympathetic nerve activity (microneurography), indicating that acute hypoxia significantly enhances muscle sympathetic activity in humans (12, 20, 21). Also, norepinephrine turnover measured directly in heart muscles from rats chronically exposed to 14 days of hypoxia is significantly elevated compared with sea level and acute altitude conditions (10). Together with the data from the present investigation, these findings show that resting skeletal muscle makes a significant contribution to the elevation found in circulating norepinephrine levels associated with prolonged exposure to high altitude.

Net release of norepinephrine from the legs increased markedly in response to submaximal exercise across all subjects and conditions. Previous investigations in both humans (22, 23) and dogs (17) have demonstrated that exercising muscles are the primary source of norepinephrine released into the plasma pool. This is supported by the results of the present investigation, and, as was found for resting values, net release during exercise was significantly greater after chronic altitude exposure compared with the other conditions. Since subjects were working at similar absolute and relative intensities during both acute and chronic exposure, it is doubtful that the exercise intensity is responsible for differences found between the two altitude conditions for net norepinephrine released. Additionally, the greater net norepinephrine release associated with chronic altitude exposure is not likely due to an increase in washout of the neurotransmitter, because blood flow to the exercising muscles was the same or lower for chronic exposure compared with the other conditions. Finally, the greater rates of norepinephrine release from exercising legs, associated with chronic exposure, were still clearly evident when corrected for the elevation found in resting values. Thus these data suggest that the sympathetic response to muscle, as determined by net norepinephrine release, is accentuated both at rest and during exercise after chronic exposure to high altitude. This response is not related to the extent of hypoxia, since net norepinephrine release by muscle was increasing, whereas arterial oxygen saturation was improving during the 21-day acclimatization period (14).

An increase in sympathetic activity to an organ is associated with an increase in norepinephrine spillover into the circulation (7, 16, 17, 27). Consequently, measurement of venous norepinephrine levels has been used as a rough estimate of total body sympathetic activity (9, 11, 24). Measurement of norepinephrine release and spillover are more accurate indicators of sympathetic nerve activity (7, 17, 23). In the present investigation a strong correlation (r = 0.95, Fig. 3) was found between arterial norepinephrine levels with that of net norepinephrine release measured both at rest and during submaximal exercise. Thus, under the conditions of the present study, measurement of arterial norepinephrine levels may serve as a valid marker of sympathetic activity; however, regional sources of spillover would remain indeterminable.

Epinephrine uptake was greatest during acute altitude exposure and most likely is related to the elevation found for arterial epinephrine levels. We have previously documented that the adrenal response and, consequently, plasma epinephrine levels are a function of the degree of hypoxia present (6, 14). Thus hypoxemia (decreased arterial oxygen saturation) was the greatest during acute exposure, yielding the greatest adrenal

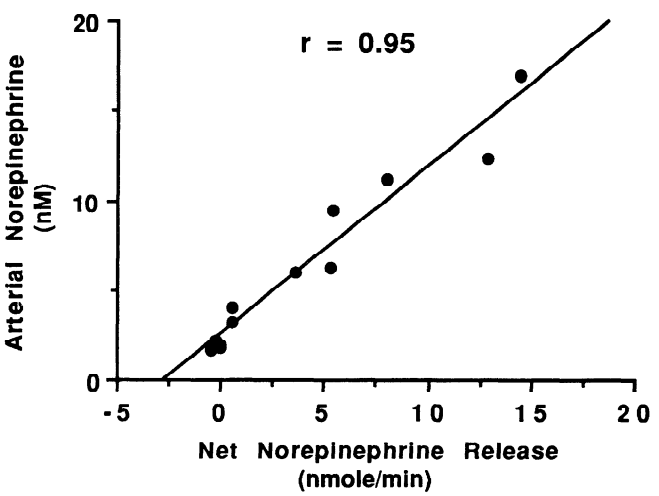

Fig. 3. Relationship between arterial norepinephrine levels and net leg norepinephrine release for all subjects (control and β-blocked) across all conditions (sea level, acute, and chronic altitude exposure) measured both at rest and during exercise.

stimulus for epinephrine release. As arterial oxygen saturation improved with acclimatization to altitude, the epinephrine levels were reduced. Net uptake of epinephrine by skeletal muscle appears to be a direct function of arterial concentration. Both at rest and during exercise, net uptake of epinephrine by skeletal muscle was directly related to arterial concentrations ($r = 0.85$).

The presence of dense β-blockade did not alter the muscle sympathetic adaptive response to chronic altitude exposure. Blocked subjects demonstrated similar patterns for norepinephrine release and epinephrine uptake by the legs as was observed in the control group. This was true for measurements made both at rest and during exercise. Differences between control and β-blocked subjects were observed primarily in lower blood flow measurements for blocked subjects both at rest and during exercise, as well as across altitude conditions (with the exception of exercise during chronic exposure when blood flows were similar). Although the lower blood flows for the β-blocked subjects at rest did not result in differences in net uptake and release of catecholamines, they may account for the reduced values for leg norepinephrine release observed during exercise at sea level and acute exposure compared with controls.

The functional significance of the elevation in muscle sympathetic activity associated with acclimatization to high altitude is reflected in a number of hemodynamic and metabolic adjustments. A relationship between increased norepinephrine levels and alterations in systemic vascular resistance (13, 15), blood pressure (26), and substrate selection and utilization (1, 2, 14) has been reported to exist with high-altitude acclimatization. The mechanisms responsible for the increase in sympathetic activity that occur over time at altitude, however, remain to be determined. Among a number of potential mechanisms, the direct effect of hypoxia on sympathetic nerve activity is not likely a cause for the response observed during prolonged exposure. As shown in this study, sympathetic activity continued to increase with time at altitude despite the finding of an elevation in arterial oxygen content with acclimatization. An increase in $\dot{V}_E$ followed a similar pattern across time at altitude with that of norepinephrine release. It is possible that the increase in $\dot{V}_E$, demonstrated to occur over time at altitude, is partially responsible for simultaneously activating sympathetic activity. Alternatively, the increase in sympathetic nerve function associated with chronic altitude exposure may be responsible for the elevation in $\dot{V}_E$. Additionally, the role that changing plasma volume and baroreceptor function play in the sympathetic response to chronic altitude exposure cannot be overlooked. Reductions in plasma volume associated with both acute and chronic high-altitude exposure could potentially stimulate sympathetic activity via the baroreceptors. Even a modest decrease in vascular volume is sufficient to elicit an increase in sympathetic nerve activity.

Finally, it must be noted that, as previously stated, leg blood flow during submaximal exercise did not differ across altitude conditions. Traditionally, an increase in muscle blood flow for a given work load has been reported when acute high-altitude exposure values are compared with sea level values in an attempt to compensate for a reduction in arterial oxygen content. The explanation for the lack of an increase in leg blood flow in the present study of exercise with acute exposure is unknown but may be related to the fact that our subjects resided the night before acute experiments at 1,954 m. It is possible that changes in plasma volume altered cardiac output and muscle blood flow during this period, which is a relatively quick adjustment to altitude exposure. However, leg $\dot{V}O_2$ was maintained during exercise at acute altitude; thus it is unlikely that oxygen delivery and utilization by exercising muscle were responsible for the sympathetic responses observed in the present study.

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