Downregulation in muscle Na\(^{+}\)-K\(^{+}\)-ATPase following a 21-day expedition to 6,194 m

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Downregulation in muscle Na\(^{+}\)-K\(^{+}\)-ATPase following a 21-day expedition to 6,194 m. J. Appl. Physiol. 88: 634–640, 2000.—To investigate the hypothesis that acclimatization to altitude would result in a downregulation in muscle Na\(^{+}\)-K\(^{+}\)-ATPase pump concentration, tissue samples were obtained from the vastus lateralis muscle of six volunteers (5 males and 1 female), ranging in age from 24 to 35 yr, both before and within 3 days after a 21-day expedition to the summit of Mount Denali, Alaska (6,194 m). Na\(^{+}\)-K\(^{+}\)-ATPase, measured by the \(^{[3]H}\)ouabain-binding technique, decreased by 13.8% [348 ± 12 vs. 300 ± 7.6 (SE) pmol/g wet wt; P < 0.05]. No changes were found in the maximal activities (mol·kg protein\(^{-1}\)·h\(^{-1}\)) of the mitochondrial enzymes, succinic dehydrogenase (3.63 ± 0.20 vs. 3.25 ± 0.23), citrate synthase (4.76 ± 0.44 vs. 4.94 ± 0.44), and malate dehydrogenase (12.6 ± 1.8 vs. 12.7 ± 1.2). Similarly, the expedition had no effect on any of the histochemical properties examined, namely fiber-type distribution (types I, IIA, IIB, I, IC, IIC, IIAB), area, capillarization, and succinic dehydrogenase activity. Peak aerobic power (52.3 ± 2.1 vs. 50.6 ± 1.9 ml·kg\(^{-1}\)·min\(^{-1}\)) and body mass (76.9 ± 3.7 vs. 75.5 ± 2.9 kg) were also unaffected. We concluded that acclimatization to altitude results in a downregulation in muscle Na\(^{+}\)-K\(^{+}\)-ATPase pump concentration, which occurs without changes in oxidative potential and other fiber-type histochemical properties.

AT THE LEVEL OF THE SKELETAL muscle cell, a number of potential adaptive strategies to chronic hypoxia have been proposed that could provide for a reasonably high ATP turnover rate while minimizing the contribution of anaerobic glycolysis. These strategies may be divided into two categories, namely those aimed at optimizing the use of O\(_2\) made available to the cell and those aimed at downregulating the ATP costs of the contractile activity (19).

In the former category, increases in mitochondrial potential have long been hypothesized as a mechanism that allowed for oxidative phosphorylation to be sus-
the number of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase pumps, whereas training in normoxia results in an upregulation (14). This finding suggests that hypoxia per se or some intracellular stimulus secondary to hypoxia is responsible for the downregulation.

In this study, our objective was to examine the effect of altitude aclimatization, occurring during an expedition to Mount Denali, on muscle enzymatic, histochemical, and Na\textsuperscript{+}-K\textsuperscript{+}-ATPase changes. We hypothesized, on the basis of earlier studies, that mitochondrial oxidative potential as measured by the maximal activities of representative mitochondrial enzymes would be downregulated in conjunction with a downregulation in the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase pumps. To determine if any of the postulated adaptations might be explained by changes in fiber-type distribution or changes in the properties of specific fiber types, we also measured a number of histochemical properties of skeletal muscle.

METHODS

Subjects. Six subjects (5 men and 1 woman) participated in the study. The males were 28 ± 2 (SE) yr old, and the female was 35 yr old. All subjects were regularly active in the months preceding the expedition, and all had a history, spread over several years, of mountain climbing. As required, all volunteers were fully informed of all procedures and the risks involved before written consent was obtained. The study was approved by the Office of Human Research and Animal Care (University of Waterloo, Waterloo, Ontario, Canada).

Experimental design. One week before the expedition, the subjects reported to the laboratory for initial measurements. These measurements included a progressive cycle test to fatigue for measurement of maximal aerobic power (VO\textsubscript{2peak}) as well as a number of other tests that examined a range of phenomena such as respiratory gas kinetics and cardiovascular and metabolic function. At this time, tissue samples were also extracted from the vastus lateralis muscle using the needle biopsy technique (1). Three days after the completion of the expedition, the subjects again reported to the laboratory for an identical series of tests, all conducted in the same sequence as the preacclimatization tests. Additional tissue samples were extracted from the vastus lateralis of the opposite leg at this time as well.

Mount Denali, which is located in Alaska, has an elevation of 6,194 m. The climb to the summit occurred over a 21-day period. On day 0, the volunteers arrived in Talkeetna, Alaska (300 m), and, on day 1, a base camp (2,160 m) was established. By day 8, the climbers attained an altitude approximately one-half of the way to the summit, and, by day 14, ~75% of the objective was realized. On day 18, ascent to the summit was achieved. By day 20, volunteers had descended to the initial base camp and returned to Talkeetna.

Analytical techniques. To measure VO\textsubscript{2peak}, a progressive test was employed as previously reported (31). This test, conducted on an electrically braked cycle ergometer (Quinton 870), consisted of progressive step increases in power output (16.3 W) each minute until fatigue. Ventilation (Ve) and gas exchange (VO\textsubscript{2} and VCO\textsubscript{2}) were determined with an open-circuit system (13) and heart rate was measured by standard electrocardiographic techniques. The VO\textsubscript{2peak} and related measures were recorded as the highest value averaged over a 30-s period. For the female subject, VO\textsubscript{2peak} values were only recorded before the expedition.

Tissue analysis. To describe the metabolic adaptations, the maximal activities of a number of enzymes representative of high-energy phosphate transfer (creatine phosphokinase), glycogenolysis (phosphorylase), glycolysis (lactate dehydrogenase, LDH), the citric acid cycle (succinic dehydrogenase (SDH), citrate synthase (CS), and malate dehydrogenase (MDH)), \( \beta \)-oxidation (3-hydroxyacyl CoA dehydrogenase (3-HAD)), and glucose phosphorylation (hexokinase) were selected for measurement. These measurements, assayed in duplicate at 22–23°C, were performed on homogenates, prepared from frozen tissue, using fluorometric techniques (18, 31). The frozen tissue was homogenized in a phosphate buffer (pH 7.4) containing 0.02% BSA, 5 mM \( \beta \)-mercaptoethanol, and 0.5 mM EDTA and diluted (1:100) in 20 mM imidazole buffer containing 0.2% BSA (18). Only in the case of SDH were the measurements made on fresh homogenates. All other enzymes were measured in homogenates that had been stored at ~80°C (18). Muscle protein was measured in triplicate using the Lowry technique as modified by Schacterle and Pollock (36).

The measurement of Na\textsuperscript{+}-K\textsuperscript{+}-ATPase was based on the vanadate-facilitated \( [\text{H}] \) ouabain-binding technique according to the procedure of Nørgaard et al. (27) and as previously published by our group (11). Two tissue samples, weighing between 2 and 8 mg, were analyzed from each biopsy. Samples in this weight range yield similar results and are reproducible (27). The concentrations of \( [\text{H}] \) ouabain (1.8 \( \mu \text{Ci/ml} \)) and ouabain (\( 10^{-8} \text{ mol/l} \)) have been previously demonstrated both in our laboratory (unpublished observations) and elsewhere (27) to produce saturable binding with similar sample sizes. All samples were corrected for loss of specifically bound \( [\text{H}] \) ouabain during washout using a factor of 1.05 (27) and for isotopic purity of the \( [\text{H}] \) ouabain (measured at 99% by the supplier, DuPont-NEN, using chromatographic techniques). We have also confirmed that, in our laboratory, washout is of a similar magnitude (unpublished observations). Samples were not corrected for nonspecific uptake and retention of \( [\text{H}] \) ouabain, which both Nørgaard et al. (27) and our laboratory (unpublished observations) estimated at <3% in human muscle.

The histochemical properties that were measured included fiber-type distribution and the area, capillarization, and oxidative potential of the different fiber types and subtypes. Details for the measurement of each of these properties appear in a recent publication from our laboratory (12). Briefly, muscle fiber typing (I, IC, IIA, IIB, IIBA, IIC) was based on tissue cross sections, cut in a cryostat (~20°C), using the basic procedures of Brooke and Kaiser (2) as modified by Staron et al. (37). Capillary identification around the different fiber types was accomplished using the lectin technique (Ulex europeaus 1) on 8-\( \mu \)m cross sections (29). Cellular oxidative potential was based on SDH activity measured in 10-\( \mu \)m cross sections according to the procedure of Pette (30) but using a single end point (15). Optical density measurements, which used an average of 25 fibers of each type (where possible), were obtained using an image analysis system (Image-Pro Plus, Media Cybernetics, Silver Spring, MD). Fiber areas, with the use of the SDH stain, were obtained using the video monitor, digitizing tablet, and tracing cursor components of the image analysis system. All samples for a given subject were run during the same analytical session. Collectively, these measurements, performed on serial cross sections, enabled determinations of the number of capillaries in contact with each fiber type and subtype (CC) and the number of capillary contacts per fiber-type area (CC/FA). Other indexes were calculated using a defined area of the cross-section. These included the number of fibers or fiber density (FD), the total number of capillaries or capillary...
density (CD), the average number of capillaries around a fiber (CAF), and the sharing factor (SF). The SF (CC/CAF) represented the quotient obtained by dividing the CAF into the average number of CC. SF is a measure of the number of fibers sharing a capillary. CAF was calculated by dividing the number of capillaries by the number of fibers (CD/FD). For these measurements, only discrete regions with clear cross sections and free of artifacts were used. The numbers of fibers and capillaries on the borders were counted and then halved. This was necessary to obtain an estimate of the absolute numbers contained with a set field, without double counting fibers and capillaries only partly in the field.

For a given subject, all samples, either for Na\(^{+}\)-K\(^{+}\) ATPase, specific enzymes, or histochemistry, were analyzed during the same analytical session.

Statistical procedures. When a single variable was involved, the data were analyzed using Student's t-tests for paired samples. In cases when more than one variable was involved (i.e., fiber type, acclimatization), a two-way ANOVA for repeated measures was employed in the analysis. When significance was indicated, post hoc analysis using the Newman-Keuls technique was used to compare specific means. The significance level was set at \(P < 0.05\) for all comparisons.

RESULTS

During the 21-day expedition to Mount Denali, no significant weight loss occurred (Table 1). Body weights measured before and 3 days after the expedition only varied by 2.3%. A reduction in \(V_\text{O}_2\text{peak}\) was evident but only when expressed in liters per minute. A similar reduction was not found when expressed relative to body weight. No change in the maximal heart rate or in reduction was not found when expressed relative to only when expressed in liters per minute. A similar change in \(\text{Na}^{+}\) wt (or 4.4%). Correlation coefficients calculated between the change in \(\text{Na}^{+}\) wt and \(V_\text{O}_2\text{peak}\) were only noted for type IIB fibers with type I fibers predominating. In only one mountaineer, both before and after the expedition, could the existence of the other fiber subtypes (IC, IIAB, IIB, and IC) be demonstrated. Altitude acclimatization also failed to alter the other fiber-type characteristics examined, namely the area, CC, CC/FA, and SDH activity (Table 3). Differences between fiber types were only noted for CC/FA and SDH; in both cases, type I fibers were greater than type IIA fibers. When the histochemical characteristics were examined in a defined area of the cross section, without regard to fiber type, no differences could be found in CD, FD, CAF, or SF with acclimatization (Table 4).

DISCUSSION

As hypothesized, we have found that a 21-day expedition to Mount Denali resulted in a downregulation of the Na\(^{+}\)-K\(^{+}\) ATPase pump concentration. However, the downregulation was not accompanied by alterations in mitochondrial oxidative potential or in the potential for high-energy phosphate transfer, glycogenolysis, or glucose phosphorylation. The maximal activity of the enzyme used to represent glycolysis, LDH, was upregulated. When the effects of the expedition were examined at the level of the specific muscle fiber types, no adaptation was found for any of the properties examined, namely percent fiber distribution, area, capillarization, and SDH activity.

It must be recognized that our measurements were performed 3–4 days after return to sea level, during which time substantial deacclimatization effects could have occurred. However, the blood level of hemoglobin displayed the typical acclimatization response with increases in concentration (15.0 ± 0.49 vs. 15.8 ± 0.41 g%) observed following the expedition. The fact that we

![Fig. 1. Changes in vastus lateralis Na\(^{+}\)-K\(^{+}\) ATPase pump concentration with acclimatization. Pre, preacclimatization; Post, postacclimatization. ■, Individual values. \(P < 0.05\) (Pre vs. Post).](http://jap.physiology.org/)
Table 2. Effect of acclimatization on muscle enzyme activities

<table>
<thead>
<tr>
<th>Protein, mg/g</th>
<th>SDH</th>
<th>CS</th>
<th>MDH</th>
<th>3-HAD</th>
<th>Phosph</th>
<th>Hex</th>
<th>LDH</th>
<th>CPK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>187 ± 2.2</td>
<td>3.63 ± 0.20</td>
<td>4.76 ± 0.44</td>
<td>12.6 ± 1.8</td>
<td>8.18 ± 0.79</td>
<td>6.04 ± 0.53</td>
<td>0.48 ± 0.04</td>
<td>36.5 ± 2.6</td>
</tr>
<tr>
<td>Post</td>
<td>192 ± 2.7</td>
<td>3.25 ± 0.23</td>
<td>4.94 ± 0.45</td>
<td>12.7 ± 1.2</td>
<td>7.48 ± 0.45</td>
<td>5.94 ± 0.61</td>
<td>0.45 ± 0.03</td>
<td>41.2 ± 3.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE in mol·kg protein⁻¹·h⁻¹; n = 6. SDH, succinic dehydrogenase; CS, citrate synthase; MDH, malate dehydrogenase; 3-HAD, 3-hydroxy-acyl CoA dehydrogenase; Phosph, phosphorylase; Hex, hexokinase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase. *Significantly different from Pre (P < 0.05).

Table 3. Altitude acclimatization and muscle fiber characteristics

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>I</th>
<th>IIA</th>
<th>IC</th>
<th>IIAB</th>
<th>IIB</th>
<th>IIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution, %</td>
<td>67.5 ± 3.9</td>
<td>29.8 ± 4.2</td>
<td>0.41 ± 0.3</td>
<td>1.8 ± 2.0</td>
<td>0.28 ± 0.3</td>
<td>0.34 ± 0.3</td>
</tr>
<tr>
<td>Area, µm²</td>
<td>73.7 ± 2.5</td>
<td>24.1 ± 1.1</td>
<td>0.27 ± 0.3</td>
<td>1.2 ± 1</td>
<td>0.81 ± 0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>CC, number</td>
<td>5144 ± 304</td>
<td>5176 ± 386</td>
<td>5122 ± 405</td>
<td>5313 ± 540</td>
<td></td>
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<tr>
<td>CC/FA, µm⁻²·10⁻³</td>
<td>6.21 ± 0.28</td>
<td>5.33 ± 0.24</td>
<td>6.08 ± 0.38</td>
<td>5.50 ± 0.33</td>
<td></td>
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</tr>
<tr>
<td>SDH activity, OD units</td>
<td>1.18 ± 0.06</td>
<td>1.04 ± 0.04</td>
<td>1.15 ± 0.05</td>
<td>1.05 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.288 ± 0.03</td>
<td>0.216 ± 0.03</td>
<td>0.273 ± 0.02</td>
<td>0.202 ± 0.02</td>
<td></td>
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</tr>
<tr>
<td>Post</td>
<td>0.306 ± 0.04</td>
<td>0.220 ± 0.04</td>
<td>0.315 ± 0.04</td>
<td>0.210 ± 0.03</td>
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</table>

Values are means ± SE; n = 5. CC, capillary contacts per fiber; CC/FA, capillary contacts-to-fiber area ratio. Main effects (P < 0.05) for fiber type were found for distribution, CC/FA, and SDH. For both CC/FA and SDH, type I > type IIA. For distribution, type I > IIA > IIAB, IIB, IIC, and IC.
expeditions (22) and Operation Everest II, a simulated acclimatization study extending over 40 days (16). In these studies, pronounced reductions in FA occurred, resulting in an increase in capillary-to-FA ratios (16, 22). Interestingly, unlike the present study, these studies also resulted in a decrease in body mass (22). The decrease in body mass could well explain the decrease observed in FA (16).

The mountaineers who participated in the Mount Denali expedition displayed a number of unique histochemical features not observed in untrained lowlanders. As an example, the vastus lateralis muscle contained an abundance of type I fibers and, with the exception of one mountaineer, no type IIB fibers or fibers containing more than one heavy chain (type IC, type IIAB, and type IIC). Typically, fiber-type distributions in the vastus lateralis of the untrained average ~50% type I, 28% type IIA, 15% type IIB, with the remainder consisting of transition fibers and particularly type IIAB (12). Given that a predominance of type I fibers has been previously reported in elite climbers (28) and that essentially no evidence exists in humans for a substantial transformation of the major fiber types to a variety of stressors (35), it would appear that a large percentage of type I fibers is a favorable characteristic for entry into mountain climbing. It should be emphasized that the fiber-type distributions reported in this study are not an artifact, since parallel samples were analyzed using tissue from an untrained subject who displayed all fiber types and subtypes.

An issue of particular interest is whether the large complement of type I fibers observed in the subjects is associated with a higher Na⁺/K⁺-ATPase content, which might provide some protection against the disturbing effects of chronic hypoxia. This does not appear to be the case. In a previous study by our group (11), the pump concentration in untrained subjects was similar to the mountaineers. Typically, untrained subjects have an approximately equal distribution of the major fiber types in the vastus lateralis (35). The fact that the concentration of the Na⁺/K⁺-ATPase does not appear to differ between the major fiber types is consistent with an earlier study in which we showed that the pump concentration varied with the oxidative potential (3).

Other histochemical properties also appeared to differ from the untrained. As an example, the number of capillaries per unit fiber area (CC/FA) and SDH activity were higher in both the type I and type IIA fibers (12). Because these characteristics are highly responsive to activity status (35), the higher values observed could well be a reflection of a history of regular exercise.

A variety of different messengers, including the circulating levels of hormones such as the glucocorticoids aldosterone and the thyroid hormones, have all been found to influence the long-term regulation of Na⁺/K⁺-ATPase. These hormones would all be expected to change at altitude (38), potentially altering Na⁺/K⁺-ATPase expression (4, 7). However, with the exception of aldosterone, which appears to show an increase during exercise following acclimatization similar to that at sea level (34), it is not clear what happens to the other hormones under similar conditions. Another hormone, insulin, remains a potential candidate given the sustained activity that occurs during the expedition and the probable reduction in circulating insulin levels (38). Chronic hypoxia has also been shown to activate the sympathetic adrenergic system, resulting in elevated norepinephrine levels (25), which also may have an effect. Disturbances in Na⁺ and K⁺ balance in the muscle cell also appear to be a potent stimulus in Na⁺/K⁺-ATPase upregulation (4, 7). Again, the problem with the acclimatization model is that these cations would probably show a greater imbalance with exercise at altitude with the stimulus favoring increased expression. Hypoxia by itself remains an attractive candidate for the downregulation given that hyperoxia, either by itself or as a result of free radical generation, appears to upregulate Na⁺/K⁺-ATPase in a variety of tissues (40). Alternatively, it is possible that the downregulation that we have observed may not be due to increased expression but rather accelerated degradation rates promoted by sustained regular daily exercise during chronic hypoxia. Although hypoxia and exercise represent two major stimuli during mountaineering expeditions, a variety of other potential stimuli also exist, such as alterations in temperature and diet, that could also influence cation pump levels.

The general lack of an effect of acclimatization on the mitochondrial enzymes of both the citric acid cycle and β-oxidation has been shown in previous studies using an 18- to 21-day period of residence at 4,300 m (17, 43). However, unlike previous studies that reported no change in LDH (43), we found LDH to be elevated. The significance of the elevation in LDH activity remains unclear. Teleologically, when considered in isolation, the higher activity should facilitate an increase in the conversion of pyruvate to lactate. This adaptation is inconsistent with what has been reported for long-term residents at altitude, namely a decrease in LDH activity (20). Although increases in hexokinase were not found in this study or in another study (43), elevations have been reported during acclimatization (17). The discrepancies that have been reported in the cytosolic enzymes with acclimatization could be due to differences in initial fitness levels of the volunteers or in the specifics of the acclimatization models. Compared with previous studies (17, 43), the volunteers used in this study were experienced mountaineers. Moreover, whereas previous studies were conducted under very controlled conditions, with regard to diet and exercise.

### Table 4. Altitude acclimatization and fiber capillarization indexes in a defined field

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
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<tbody>
<tr>
<td>CD, capillaries/mm²</td>
<td>709 ± 19</td>
<td>693 ± 29</td>
</tr>
<tr>
<td>FD, fibers/mm²</td>
<td>320 ± 29</td>
<td>330 ± 36</td>
</tr>
<tr>
<td>CAF, capillaries/fiber</td>
<td>2.27 ± 0.19</td>
<td>2.17 ± 0.23</td>
</tr>
<tr>
<td>SF, fibers/capillary</td>
<td>2.59 ± 0.10</td>
<td>2.65 ± 0.09</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 5. CD, capillary density; FD, fiber density; CAF, capillaries per fiber; SF, sharing factor.
patterns, the present study involved a mountaineering expedition to substantially higher altitudes.

Earlier studies using a much more sustained and severe period of acclimatization either as part of a mountaineering expedition (23) or during chronic hypobaria as in Operation Everest II (16) reported pronounced reductions in the maximal activities of enzymes involved in mitochondrial function, whereas cytosolic enzyme activities remained unaltered. Such an effect also appears to occur in natives resident to high altitude (6). Interestingly, when these residents are subjected to regular exercise either in their native hypoxic environment or during normoxia, pronounced increases in mitochondrial potential occur (6).

Training in normobaric hypoxia while resident at sea level appears to potentiate the stimulus for the expression of mitochondrial enzymes over the same absolute amount of training in normoxia (26, 39). Conceivably, the increased expression of the mitochondrial enzymes is due to the greater metabolic imbalance associated with performing exercise in an O$_2$-deprived intracellular environment (41). As has been shown earlier (14), the Na$^+$-K$^+$-ATPase does not respond the same way.

Unclear from the present study is what functional role the reduction in Na$^+$-K$^+$-ATPase pump concentration has. Unfortunately, given the amount of tissue available, measurements of Na$^+$-K$^+$-ATPase activity could not be performed. We were also not able to determine if the binding affinity for $[^3]H$ouabain was altered in conjunction with the downregulation in the number of pumps. However, previous studies that used both exercise training, which results in an upregulation (24), and chronic heart failure, which results in a downregulation (32) of the pumps, reported that only a single population of $[^3]H$ouabain binding sites exist. If such is the case, the downregulation in Na$^+$-K$^+$-ATPase pumps that we have reported in the present study would be expected to result in a depression in the maximal Na$^+$-K$^+$-ATPase activity and an impaired potential to reestablish Na$^+$ and K$^+$ gradients across the sarcolemma during challenging contractile activity (5). Because we have found only minimal changes in whole body VO$_2_{peak}$ with acclimatization, similar to what was reported earlier (42), the downregulation would not appear to have any significance on this measure. Increases in leg VO$_2_{peak}$ would also not be expected, since the dominant changes in VO$_2$ with exercise occur in working leg muscles (8). Our results suggest that excitation of the sarcolemma and T tubules can be preserved during progressive exercise to a level sufficient to realize a VO$_2_{peak}$ despite the reduction in Na$^+$-K$^+$-ATPase concentration observed following acclimatization.

In summary, this study appears to be the first to demonstrate that the muscular adaptations realized during a mountaineering expedition occur not by an upregulation of mitochondrial oxidative potential but by a downregulation of one of the cation pumps, namely the Na$^+$-K$^+$-ATPase. Although it is inviting to credit the observed change in Na$^+$-K$^+$-ATPase to chronic hypoxia, other factors may be implicated. The mountaineering expedition involved exposure to a wide variety of stressors, including exercise, dietary alterations, and cold, all of which could affect the acclimatization responses. Despite the limitation imposed by the small number of mountaineers available for study, the observation that Na$^+$-K$^+$-ATPase is significantly downregulated provides a unique and exciting focus for additional work examining the adaptation in skeletal muscle to chronic hypoxia.

Special appreciation is extended to the mountaineers who so generously volunteered to participate in the study. The expert technical assistance provided by Dr. Jing Ouyang is gratefully acknowledged.

This study was supported by grants from the National Sciences and Engineering Research Council of Canada and from the Ottawa Heart Institute.

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Received 26 May 1999; accepted in final form 22 October 1999.

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