

Effects of Chronic Hypoxemia on the Afferent Nerve Activities from Skeletal Muscle

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An acute reduction of the oxygen supply to contracting muscles not only affects their metabolism but also modifies their sensorimotor control through changes in afferent discharge of the group I and group III–IV nerve fibers, the latter playing a pivotal role in the protective mechanisms against muscle fatigue. The effects of chronic hypoxemia on the muscle sensitivity are totally unknown. In the present study, group I fibers (mechanosensory afferents) and group III–IV fibers (mechanosensory and chemosensory afferents) from the anterior tibial muscle were recorded in normoxic and chronic hypoxic rats. Hypoxic rats breathed for 45 d a gas mixture containing 9.5 to 10% O₂ in N₂. The data were compared with those obtained in normoxic animals of the same age. To activate the different muscle afferents, we used different test agents, including electrically induced fatigue (EIF), KCl, lactic acid injections, as well as tendon vibrations. The conduction velocity of all nerve fibers was significantly ($p < 0.01$) higher in hypoxic rats than in the normoxic group. Chronic hypoxemia significantly depressed the response of the group III–IV muscle afferents to KCl injections and even abolished their response to lactic acid and EIF. However, the response to tendon vibrations of the group I afferents was similar in hypoxic and normoxic rats. These results suggest that chronic hypoxemia markedly alters the chemosensitivity of the group III–IV muscle afferents, which may explain the higher fatigability of hypoxic subjects.

Keywords: chronic hypoxemia; muscle efferent fibers; neuromuscular fatigue; rats; sensory motor control

Animal studies in resting limb muscles have shown that the group III–IV muscle afferents are markedly activated by an acute reduction of the oxygen supply produced either by a reduction of muscle blood flow (ischemia) (1, 2) or by a decrease in oxygen partial pressure in arterial blood (hypoxemia) (2–4). Moreover, we observed (5) that the group III–IV phrenic afferents are (also) markedly activated by ischemia during spontaneous diaphragmatic contractions. By contrast, hypoxemia and ischemia significantly attenuate the activation of muscular mechanoreceptors (group I fibers) by tendon vibrations (2). In a recent animal study (3), we showed that acute hypoxemia depresses and even abolishes the response of the group IV muscle afferents to electrically induced muscle fatigue (EIF), a situation which markedly activates these sensory endings in the skeletal muscles (6–8) as well as in the diaphragm (9) in normoxic animals. However, no data exist on the consequences of chronic hypoxemia on muscular afferent activities.

Several studies in healthy humans have documented the fact that acute (10–12) as well as chronic (13) hypoxemia re-

duces the endurance to fatigue and also diminishes the leftward shift of the electromyographic (EMG) power spectrum during sustained static contractions of both skeletal muscles (10–13) and the diaphragm (10). In addition, one study of hypoxic patients with chronic respiratory insufficiency (14) has shown that the recovery on reoxygenation of these patients not only markedly improves their endurance to fatigue but also changes the high-to-low ratio of EMG energies during sustained contractions of both the diaphragm and skeletal muscles. This suggests that the recruitment of motor units may be altered in chronic hypoxemia. The changes in the EMG power spectrum are measured by the decrease in median frequency that divides the power spectrum into two regions of equal power. A decrease in median frequency is attributed to reflex inhibitory effects exerted by the group III–IV muscle afferents on motoneurons driving the fast, fatigable motor units (9, 15, 16). It may be deduced from the aforementioned observations that acute as well as chronic hypoxemia reduces the endurance to fatigue during fatiguing contractions through a reduced recruitment of slow, i.e., fatigue-resistant, motor units.

In the present study, we examined the response of nerve afferents of a limb muscle (musculus tibialis anterior) to different test agents, and to electrically induced contractions in rats acclimatized for 45 d to hypoxemia. Data were compared with those obtained in animals of the same age placed in normoxic condition.

METHODS

Animals and Chronic Hypoxic Condition for the Experimentation

The experimental protocol was approved by the institutional care and use committee. Eleven female Wistar rats (body weight, 190 to 200 g) (Iffa Credo, Les Oncins, France) were left 45 d in a Plexiglas cage (length, 84 cm; width, 40 cm; height, 40 cm). Excrements and urine fell in a second compartment, regularly washed by water. Several sealed air locks were placed on the cage side. One air lock was used to give water and food *ad libitum*. Through the others, O₂ and CO₂ concentrations were measured (polarographic O₂ analyzer, Diltroic KE50, St. Germain en Laye, France; and infrared CO₂ analyzer, Godart-Statham, Bilthoven, The Netherlands). CO₂ was absorbed by soda lime and the concentration was less than 0.04%. Relative humidity was regulated by absorbing water with calcium chloride granules, and it was maintained between 45% and 50%. The cage temperature was measured and remained stable ($25 \pm 1^\circ \text{C}$).

To reduce the oxygen concentration in the ambient air, an oxygen extractor (Zefir Plus; L'Air Liquide, Le Plessis Robinson, France) was modified to keep only the nitrogen fixed by the molecular filter, and then to reinject it in the gas flow stream propelled with a compressor. A flow meter allowed us to vary the amount of nitrogen-enriched mixture and thus to adjust the oxygen concentration of the gas flow stream injected into the cage. The cage was continuously swept out by a gas flow stream containing 9.5% to 10% oxygen in nitrogen.

A second group of 10 Wistar female rats of the same age was kept in the same room and breathed ambient air. At the end of the electro-

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physiologic investigations, animals from the two experimental groups were killed with an overdose of anesthetics.

Surgery and Nerve Recordings

Surgery was carried out on the animals under pentobarbital anesthesia (Nembutal, 60 mg · kg⁻¹, intraperitoneally, Sanofi, France). Atropine (1 mg · kg⁻¹, intraperitoneally) was administered to reduce the airway secretions. A tracheotomy was performed and rats were artificially ventilated at constant volume (rate 40 to 60/min, tidal volume 2 to 4 ml, Harvard, Southmatick, MA). To maintain hypoxemia throughout surgery and nerve recordings, the chronic hypoxic rats were ventilated with a hypoxic mixture (10% O₂) whereas the normoxic rats were normally ventilated with room air. The right femoral vein was cannulated to allow a supplemental administration of anesthetic and of pancuronium bromide (Pavulon, 10 mg/kg; Organon Technika, Fresne, France). The contralateral femoral artery was catheterized to sample blood (0.3 ml) for blood gas analyses (ABL330 Radiometer, Copenhagen, Denmark) and to measure hematocrit. Blood pressure was also measured with an electromanometer (model P23Db; Statham, Puerto Rico). The arterial catheter allowed us to inject retrogradely KCl (0.5 ml) and lactic acid (0.1 ml) at different concentrations (1, 5, 10, 20 mM for KCl; and 0.5, 1, 2, 3 mM for lactic acid). Throughout the operative procedure, the level of anesthesia was continually assessed by monitoring the blood pressure and the heart rate. Supplementary doses of anesthetic (Nembutal 4.8 mg/kg intravenously, Sanofi, France) were given at hourly intervals to maintain the systolic arterial blood pressure between 100 and 120 mm Hg.

The right anterior tibial muscle was dissected and freed from the surrounding tissues, and the tendons were left intact. The knee and ankle were firmly held by clamps on a horizontal support to avoid limb motions during direct electrical muscle stimulations. To measure the strength of the muscle contraction, a steel hook was implanted in the distal tendon and connected to an isometric strain gauge (Microdynamometer S 60; Ugo Basile Narco Biosystem, Houston, TX). The output signal of the strain gauge was fed to a chart recorder (model TA4000; Gould, Ballainvilliers, France).

As previously described (3, 6, 8), dissection at the middle thigh level was carried out to expose the common peroneal nerve. Using microsurgical techniques and an operating microscope (×40, OPM 11; Zeiss, Oberkochen, Germany), a longitudinal incision was made along the lateral thigh and upper leg. Then, the peroneal nerve was dissected free from surrounding tissues at a length of 40 mm and its proximal portion was cut. The cut nerve was desheathed and its distal portion placed on bipolar platinum electrodes for stimulation. Shocks were delivered by a neurostimulator (model S88; Grass, Quincy, MA) through an isolation unit. To record the activity from the muscle afferents, small strands were teased and placed on individual monopolar tungsten electrodes referred to a nearby ground. Nerve activities were amplified (2 to 50 K) and filtered (30 to 10,000 Hz), then sent to an oscilloscope (DSO 400; Gould) coupled with an XY recorder (XY Colorwriter 6120; Gould) and to the chart recorder (model TA 4000; Gould). Nerve activities were also stored on magnetic tape (RD 125 T; TEAC, Tokyo, Japan) for further analyses which consisted of discriminating the action potentials, which counted for 1-s consecutive epochs.

The afferent discharge was displayed on the chart recorder and the action potentials fed into two pulse window discriminators, built in our laboratory, which simultaneously analyzed two different afferent populations. The output of these discriminators provided noise-free tracings (discriminated units), which were counted by two different frequency meters at 1-s intervals (rate of discharge of discriminated units = f impulses, s⁻¹) and then displayed on the chart recorder. The discriminated units were counted and recorded on separate tracings. Because of the small size of action potentials of the thin afferent fibers in each bundle, the window discriminators allowed us to select two to three units in each afferent population, i.e., four to six units per filament bundle, and to study the activities of the afferent populations. The discriminated units were also displayed on a storage oscilloscope (DSO 400; Gould) to average the nerve action potential evoked by the stimulation of the distal nerve with single shocks (1-ms-long supramaximal rectangular pulses) delivered by the Grass S88 stimulator.

The following procedures were performed for each selected filament bundle:

1. Recording of the compound nerve action potential: the whole nerve trunk was stimulated distally with single shocks (0.1-ms to 1-ms rectangular pulses, supramaximal voltage), and conduction velocities were calculated in each filament bundle from the ratio between the interelectrode distance and the stimulus–response latency. The conduction velocities of the different afferent fibers were calculated using an interelectrode distance of 1.5 cm.
2. Determination of the receptive field: for filaments containing either spontaneously active or silent fibers, the belly of the anterior tibial muscle was touched with a blunt rod to ensure that the afferent activity recorded was initiated in this muscle.
3. The response of the afferent units to test agents: the group III–IV afferents were identified through their activation by intra-arterial bolus injections of KCl and lactic acid and by EIF. Mechanoreceptors were activated by tendon vibrations.

At the end of experiment the anterior tibial muscle was removed and weighted. The animals were killed by injections of lethal doses of anesthetic.

Test Agents Used to Activate Muscle Afferents

To elicit EIF, rhythmic muscle contractions were produced by a neurostimulator (model S8800; Grass) which delivered rectangular pulse trains to a pair of steel hooks implanted in the muscle (pulse duration: 0.1 ms; frequency: 10 Hz, i.e., 5 shocks in each 500-ms train; duty cycle: 500/1,500 ms). The voltage was supramaximal, i.e., 20% higher than that used to elicit a twitch. The muscle fatigue was assessed from the decay of force throughout the 3-min EIF period. The discharge rate of the nerve afferents was averaged for a 1-min period preceding EIF (control), and its maximal change was measured during the first 2-min period after EIF.

Different concentrations of KCl and lactic acid were used to establish relationships between the doses and the nerve discharge. A catheter was inserted into the contralateral artery and advanced retrogradely as far as the fork of the abdominal aorta. It was positioned so that the blood flow to the studied anterior tibial muscle was not interrupted. At the end of the experiment, we verified that the catheter tip was adequately placed.

After identifying an afferent population of fibers whose endings were in the anterior tibial muscle, varying amounts of KCl (1, 5, 10, and 20 mM) and lactic acid (0.5, 1, 2, and 3 mM) were injected into the artery while the nerve activities were continuously recorded in the selected afferent units. Each injection required 5 to 10 s to be completed, then normal saline (0.5 ml) was injected to wash the catheter. The control discharge rate of the afferents was averaged for the 1-min period preceding each drug injection. For each filament bundle, the peak increase in discharge rate after each injection was measured and dose–response curves were established for KCl and lactic acid.

A commercially available vibrator (Ling Dynamic System, Baldock, UK), driven by a frequency generator, delivered rectangular mechanical shocks perpendicularly to the longitudinal muscle axis. Vibrations were applied for 10-s periods. The vibration frequency increased step-by-step from 10 to 100 Hz, while the discharge of single afferent units was recorded. The optimal frequency for the mechanical vibrations to elicit the maximal discharge rate was determined for each filament bundle.

Statistical Analysis

Significant changes in the afferent activity induced by each test agent were determined with respect to the corresponding averaged control values. Mean values of firing rate (F_{impulses} , in impulse · s⁻¹) are given ± SEM and their variations are expressed as a percentage of the corresponding control discharge rate, in order to compare different values from different recordings of nerve populations. Statistical analyses were performed with a commercially available software program (SigmaStat, Jandel, Germany). A nonparametric, paired two-tailed P test (Wilcoxon signed-rank test for pair) was used. Differences were considered significant when $p < 0.05$.

RESULTS

The values of hematocrit and arterial blood gases measured during the surgery and anesthesia are shown in Table 1. In

TABLE 1. HEMATOCRIT, ARTERIAL BLOOD GASES, AND NORMALIZED MUSCLES MASS (TIBIALIS ANTERIOR) MEASURED IN CONTROL NORMOXEMIC RATS AND IN ANIMALS OF THE SAME AGE THAT BREATHED FOR 45 D A HYPOXIC GAS MIXTURE ($F_{I_{O_2}} = 10\%$)*

	Normoxemia	Chronic Hypoxemia
Hematocrit, %	46 ± 1	65 ± 1 [†]
Pa _{O₂} , mmHg	112 ± 6	44 ± 1 [†]
Pa _{CO₂} , mmHg	37 ± 2	28 ± 2 [‡]
pHa	7.50 ± 0.01	7.41 ± 0.01
Sa _{O₂}	98 ± 0.3%	82.6 ± 1.6 [†]
Muscle weight/rat weight	2.75.10 ⁻³ ± 3.10 ⁻⁴	3.10 ⁻³ ± 4.10 ⁻⁴

* Values are expressed as mean ± SEM.

[†] p < 0.001.

[‡] p < 0.01.

chronic hypoxemic rats, hematocrit was significantly higher than in control animals (+29%, p < 0.001). This assesses the efficiency of the hypoxia chamber. These data also show that hypoxemia was maintained in chronic hypoxemic animals throughout the period of surgery and nerve recordings. No intergroup differences in muscle weight, normalized by the animal weight, were noted.

Peaks of the compound nerve action potentials reflect the proportion of group fibers within the nerve. Although these data are not crucial to the understanding of the results, we estimated the proportion of fibers in the whole nerve and compared this proportion between normoxemic and chronic hypoxemic rats. Measurement of each peak size allows one to estimate the relative proportions of the different nerve afferents. A total of 130 afferent nerve fibers were recorded. In the control group 64 afferent fibers were recorded (87% were activated by KCl and lactic acid). In chronic hypoxemic rats, 66 afferent fibers were recorded (67% responded to KCl and lactic acid). In chronic hypoxemic rats, higher conduction velocities were measured in group I (+242%, p < 0.01), group II (+159%, p < 0.01), and group IV nerve fibers (+154%, p < 0.01), the variations being markedly accentuated in large myelinated fibers (Figure 1).

As shown in Figure 2, EIF significantly (p < 0.001) activated the muscle afferents in normoxemic animals (+139%) but not in hypoxemic ones, the intergroup difference being highly significant (p < 0.001).

In hypoxemic rats, the response of the group III–IV afferents to KCl and lactic acid differed from that measured in normoxemic rats (Figure 3). In the control group, there was a relationship between the doses of KCl and the change in

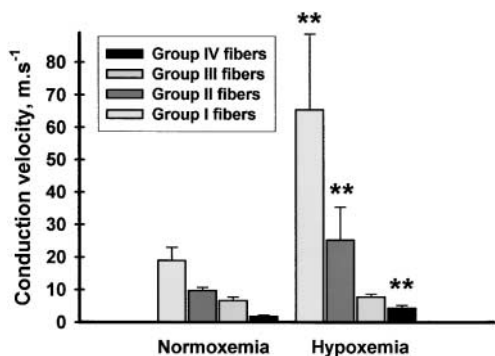


Figure 1. Conduction velocity of afferent nerve fibers, measured after prolonged exposure to hypoxia and compared with the values found in normoxemic rats. Asterisks show significant differences between the normoxemic and hypoxemic conditions. (**p < 0.01).

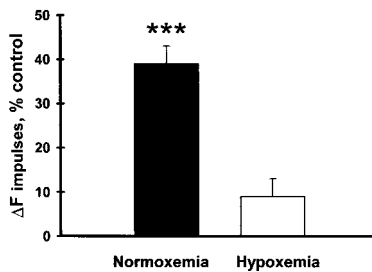


Figure 2. Afferent nerve response to EIF. The post-EIF changes in afferent discharge rate ($\Delta F_{impulses}$) are only significant in normoxemic rats (**p < 0.001). The differences between normoxemic and chronic hypoxemic rats are significant (p < 0.001).

discharge rate, whereas their activation by lactic acid culminated for the lowest concentrations. In chronic hypoxemic rats, the response of the group III–IV muscle afferents to KCl was markedly depressed and even suppressed for the highest concentrations. Lactic acid injections failed to activate these afferents.

In normoxemic and hypoxemic rats, an increased discharge rate of muscle afferents in response to the mechanical vibrations was present and a plateau response was measured when the vibration frequency reached 50 Hz (Figure 4). In chronic hypoxemic rats, a modest but significant reduction of the nerve response was measured at 20 Hz (–23%, p < 0.05) and 30 Hz (–26%, p < 0.01).

DISCUSSION

The present study shows that, compared with normoxemic rats of the same age, a prolonged reduction of oxygen supply (chronic hypoxemia) markedly decreases the response of the group III–IV muscle afferents to their specific stimuli and, by

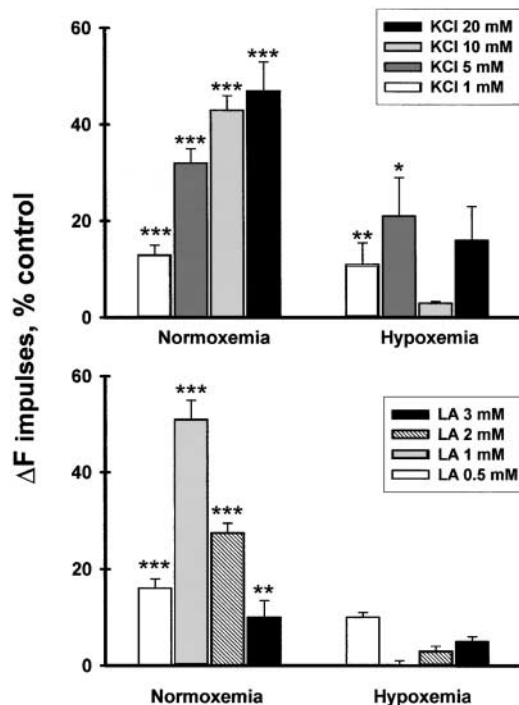


Figure 3. Afferent nerve response to KCl and lactic acid (LA). The changes in discharge rate ($\Delta F_{impulses}$) are measured after a stepwise increase in KCl or LA concentration. Asterisks indicate significant changes compared with the resting discharge rate (*p < 0.05; **p < 0.01; ***p < 0.001). Compared with normoxemic rats, hypoxemia attenuates the nerve responses to KCl 5 mM, 10 mM, and 20 mM (p < 0.001), and also to LA 0.5 mM (p < 0.01), LA 1 mM and 2 mM (p < 0.001), LA 3 mM (p < 0.05).

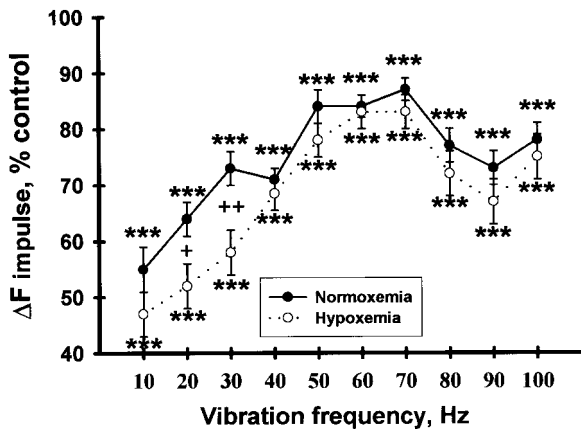


Figure 4. Afferent nerve response to tendon vibration. Tendon vibrations elicited a stable increase in the afferent nerve discharge, the peak activity varying with the vibration frequency. The general pattern of response was similar in the two groups of rats. Asterisks indicate that the vibrations increase significantly the control resting discharge (** $p < 0.001$). Compared with normoxemic animals, hypoxemia only reduces the nerve response to vibrations at 20 Hz ($+p < 0.05$) and 30 Hz ($++p < 0.01$).

contrast, elicits few changes in the response of the muscular mechanoreceptors to the mechanical vibrations. Furthermore, all nerve fibers recorded in hypoxemic animals have higher conduction velocities than those measured in control animals. The following discussion will focus on the mechanisms of the altered muscular sensitivity after acclimation to hypoxemia, a situation encountered in subjects living at high altitude and in patients with chronic respiratory insufficiency.

An increased conduction velocity in myelinated and, to a lesser extent, unmyelinated nerve fibers could be explained by the fact that hypoxemia activates ATP-sensitive K^+ channels (17, 18), facilitating the membrane depolarization.

Our data indicate that the pattern of afferent nerve response to the mechanical vibrations was similar in chronic hypoxemic and normoxemic rats. This opposes previous observations in cats (2), which showed that acute hypoxemia and muscle ischemia markedly depressed the response of mechanosensitive afferents to vibration. However, Pa_{O_2} was very low in our previous study, i.e., 20 mm Hg, compared with 44 mm Hg in the present one. Thus, we may suppose that the afferent nerve pathways detecting the changes in muscle fiber length are not affected by chronic hypoxemia and that the facilitating reflex influence controlling the motoneuron discharge is still effective in hypoxemic individuals.

It was shown in normoxemic rabbits (3, 6, 7, 19), rats (8), and cats (9) that the group III–IV afferent discharge significantly increased after EIF. In addition, dose-dependent relationships between the group III–IV discharge rate and the lactic acid or KCl concentrations have already been reported in normoxemic rats (8) and cats (20), and they are also found in the present study in normoxemic rats. The responses provided by the chemicals have never been studied previously in a chronic hypoxemic condition. The present study shows that all chemicals used to activate muscle endings connected with the group III–IV fibers were ineffective in increasing the discharge rate in chronic hypoxemic rats, compared with the nerve responses measured in normoxemic animals. Namely, in hypoxemic rats, the group III–IV afferents did not respond to the highest concentrations of KCl and to the different doses of lactic acid. Moreover, the activation of the group III–IV afferents after EIF in chronic hypoxemic rats was 1.5 times lower

than that measured in normoxemic animals, corroborating recent data in rabbits exposed to acute hypoxia (3). Thus, the inhibitory influence of hypoxemia on the group III–IV muscle afferents not only concerns their response to a complex pathophysiological circumstance (i.e., muscle fatigue), known to activate these nerve fibers through the endogenous release of potassium, lactic acid, and inflammatory mediators (6, 21), but it also concerns their response to deposits of exogenous KCl and lactic acid in the muscle.

Therefore, the hypoxemia-induced depressed response of the group III–IV afferents cannot be solely attributed to changes in muscle metabolism in hypoxemic condition. Indeed, it is commonly observed that general hypoxemia does not markedly increase muscle lactate concentration in animal and human skeletal muscles at rest (22, 23). At a given exercise intensity, acute hypoxemia in humans (23, 24) and animals (25, 26) increases the blood lactate concentration, but this is not true in subjects acclimated to hypoxia. Moreover, after acclimation to high altitude the blood lactate concentration at a given work load tends to return to values measured at sea level (27). The explanations for a reduced production of lactate by contracting muscle fibers in chronic hypoxemic subjects may be the following: an increased mobilization and use of free fatty acids, which results in reduced anaerobic paths and sparing of muscle glycogen (28, 29); and changes in proportion of muscle fibers (muscle plasticity). However, conflicting data are found in the literature. Some animal studies suggest that chronic hypoxemia modifies the muscular metabolic paths toward an increased level of oxidative enzymes (30). By contrast, human studies in sea-level natives acclimated to high altitude (31, 32) and in high-altitude natives (33) do not confirm the animal observations and even suggest that high-altitude natives have a reduced capillarity and muscle tissue oxidative capacity compared with sea-level natives (33). In patients with chronic respiratory insufficiency, biochemical studies showed reduced ATP and phosphocreatine (PCr) contents in skeletal muscles at rest and a lowered recovery of PCr re-synthesis after exercise (34). This suggests an impairment of the cellular metabolism related to hypoxemia.

The aforementioned observations of an hypoxemia-induced reduction of the muscle metabolism may explain the fact that EIF failed to activate the group III–IV muscle afferents in chronic hypoxemic condition. However, this cannot explain the reduction and even the absence of activation of these nerve endings by exogenous KCl and lactic acid. Thus, it seems that the transduction properties of these sensory nerve endings are altered in hypoxemic condition. An alteration of ATP-sensitive K^+ channels by hypoxemia (17, 18) may explain the depressed afferent nerve responses to KCl injections. It is well known that severe hypoxemia increases the baseline discharge of the group III–IV afferents in cats (2) and rabbits (3). The fact that hypoxemia increased the baseline activity of the group III–IV afferents may affect their responses to KCl and lactic acid. Thus, we may suppose that the discharge rate of these afferents was already near maximal with no possible further activation by KCl and lactic acid.

Another explanation for the reduced activation of group III–IV afferents in resting as well as contracting muscle in hypoxemic condition is the enhanced local synthesis of adenosine and nitric oxide (NO) by the endothelium and also the muscle fibers in hypoxemic condition (35). Indeed, a recent electrophysiologic study in rabbits (19) demonstrated that an increased endogenous NO production in limb muscles markedly depresses the resting discharge rate of group III–IV muscle afferents and attenuates their activation by EIF. There is no information on an eventual direct effect of NO on the mus-

cular nerve endings. It may be supposed that the inhibitory effects of NO on the group III–IV afferents are mediated through the associated changes in muscle blood flow (36) and/or the NO-induced depression of muscle energetics (37, 38).

Our animal observations suggest that people living at high altitude or suffering from chronic respiratory insufficiency are unable to detect the metabolic changes occurring in contracting skeletal muscles, and thus, to anticipate muscle failure through the activation of reflex loops which regulate the motor drive to muscles. This ineffectiveness of sensorimotor control is already documented in healthy humans under acute (10–12) and chronic hypoxemic situations (13). This may explain the observations of reduced endurance time to fatigue reported in subjects acclimated to high altitude (13, 39, 40) and in patients with severe chronic respiratory insufficiency (14).

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