Exercise delays the hypoxic thermal response in rats


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Exercise delays the hypoxic thermal response in rats. J Appl Physiol 95: 272–278, 2003. First published March 7, 2003; 10.1152/japplphysiol.00057.2003.—Exercise exacerbates acute mountain sickness. In infants and small mammals, hypoxia elicits a decrease in body temperature (Tb) [hypoxic thermal response (HTR)], which may protect against hypoxic tissue damage. We postulated that exercise would counteract the HTR and promote hypoxic tissue damage. Tb was measured by telemetry in rats (n = 28) exercising or sedentary in either normoxia or hypoxia (10% O2, 24 h) at 25°C ambient temperature (Ta). After 24 h of normoxia, rats walked at 10 m/min on a treadmill (30 min exercise, 30 min rest) for 6 h followed by 18 h of rest in either hypoxia or normoxia. Exercising normoxic rats increased Tb (°C) vs. baseline (39.68 ± 0.99 vs. 38.90 ± 0.95, mean ± SD, P < 0.05) and vs. sedentary normoxic rats (38.0 ± 0.99, P < 0.05). Sedentary hypoxic rats decreased Tb (36.15 ± 0.97 vs. 38.0 ± 0.36, P < 0.05) whereas Tb was maintained in the exercising hypoxic rats during the initial 6 h of exercise (37.61 ± 0.55 vs. 37.72 ± 1.25, not significant). After exercise, Tb in hypoxic rats reached a nadir similar to that in sedentary hypoxic rats (35.05 ± 1.69 vs. 35.03 ± 1.32, respectively). Tb reached its nadir significantly later in exercising hypoxic vs. sedentary hypoxic rats (10.51 ± 1.61 vs. 5.36 ± 1.83 h, respectively; P = 0.002).

Significantly greater histopathological damage and water contents were observed in brain and lungs in the exercising hypoxic vs. sedentary hypoxic and normoxic rats. Thus exercise early in hypoxia delays but does not prevent the HTR. Countering the HTR early in hypoxia by exercise exacerbates brain and lung damage and edema in the absence of ischemia.

cerebrospinal fluid; hypoxic tissue damage; cerebral edema; pulmonary edema; altitude illness

ACUTE MOUNTAIN SICKNESS (AMS) occurs in humans ascending above 2,500 m. AMS results from ascending too high too fast. Symptoms of AMS include headache, dizziness, nausea, insomnia, fatigue and/or lassitude, and vomiting (16). In some cases, AMS may progress to lethal high-altitude cerebral edema (HACE) and/or high-altitude pulmonary edema (HAPE) (18). Every year, 30 million people visit moderate altitudes (1,500–2,500 m) in the American West. With an incidence of AMS of 15–25%, four to eight million people are affected by AMS every year such that AMS represents a considerable public health problem with serious economic ramifications (16). Roach et al. (26) have reported that exercise early in hypoxia causes a greater than threefold rise in AMS symptom severity in humans. Elevated body temperature (Tb) secondary to exercise may promote damage to brain, lungs, and other tissues during sustained hypoxia. Maggiorini et al. (22) have demonstrated a relationship between Tb and symptoms of AMS in humans at altitude.

Infants and small mammals reduce metabolic rate and Tb in response to hypoxia. This regulated hypoxic thermal response (HTR) (10, 14, 27) is an allometric function of body mass with larger animals less likely to display the response (9). The HTR has been reviewed recently (10, 27). Most studies of the HTR have involved brief exposures to hypoxia ranging from 10 to 30 min (10, 27). The introduction of telemetry has allowed study of Tb responses in conscious, unrestrained animals during more prolonged hypoxia such that the full expression of the HTR can be analyzed (3, 4, 24). We have shown that the amplitude and duration of the HTR is dependent in rats on ambient temperature (Ta), with greater and more prolonged decreases in Tb occurring at cooler Ta values (4). In Sprague-Dawley rats entrained to 12-h light-dark cycles, exposure to a 63-h period of sustained hypoxia (10% O2 in N2) leads to a rapid decline of Tb over several hours depending on the ambient Ta with abolition of circadian oscillations of Tb and locomotor activity. At Ta 21°C, the decline of Tb is on the order of ~6°C attained at ~6 h after the hypoxic challenge. Circadian oscillations of Tb and locomotor activity return promptly on restoration of normoxia (3, 4).

We have reported that brain damage is more likely to occur in rats exposed to sustained hypoxia at a Tb of 29°C, normally a thermoneutral temperature in normoxic rats (13), compared with rats exposed to hypoxia at Tb values of 25 or 21°C (19, 20). At a Tb of 29°C, the HTR is essentially absent (3, 4). This observation suggests that the HTR provides protection to vulnerable organs early during hypoxia. There are increased sur...
survival rates in animals exposed to hypoxia at cooler \( T_a \) values, and hypoxic animals seek cooler \( T_a \) values (27, 28). Because the HTR is greater in amplitude and duration at cooler \( T_a \) values, the degree of organ protection should be greater than when hypoxia is elicited at warmer \( T_a \) values. The HTR is temporary and likely provides organ protection in small mammals early in hypoxia until respiratory acclimatization mechanisms augment tissue \( O_2 \) delivery (25). The central hypothesis is that when the HTR is limited either by a higher \( T_a \) or by imposition of an exercise challenge early in hypoxia, the level of cellular hypoxia is greater for a given level of inspired \( O_2 \) owing to higher tissue metabolic rates, thereby increasing the probability of hypoxic tissue injury.

The purpose of the present study was to investigate in rats the effect of an exercise challenge imposed during the initial 6 h of exposure to sustained hypoxia both on the HTR and on indexes of cerebral and pulmonary morphological damage as well as brain and lung water contents.

METHODS

Studies were performed on male Harlan Sprague-Dawley rats weighing between 350 and 450 g. This investigation was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the University at Buffalo.

Instrumentation

The rats were anesthetized with ketamine (80 mg/kg) and xylazine (16 mg/kg), and a calibrated telemetry probe (Mini-mitter, Bend, OR) was implanted in the abdominal cavity under aseptic conditions for measurement of \( T_b \). Postoperatively, rats were given buprenorphine (0.05 mg/kg im) for analgesia. After 3 days of recovery from surgery, the rats were placed in a soundproof environmental room with 12:12-h light-dark cycles. The light period was from 0600 to 1800. The rats were acclimated to a \( T_a \) of 25°C for 1 wk before data collection. Food and water were provided ad libitum, and all rats were eating and drinking at the time of study as described previously (3, 4).

Data Collection

Two sealed treadmills (Columbus Instruments, Columbus, OH) enclosed in Plexiglas and placed in the environmental room at a \( T_a \) of 25°C were used in this study. A single rat was studied in each treadmill. A telemetry receiver placed on top of a treadmill measured the average frequency output from the implanted abdominal probe every 6 min over a 48-h period. The receivers were connected to a multiplexer that in turn was connected to a microcomputer in an adjacent room that converted frequency output to temperature. Data were analyzed and stored by using Vital View software.

Hypoxia

Normobaric hypoxia (10% \( O_2 \) in \( N_2 \)) was induced by delivering a mixture of air and \( N_2 \) into the sealed treadmill at a rate of 6 l/min. Hypoxia was initiated on the second day of testing beginning at 0700 and was sustained for a period of 24 h. Treadmill inspired \( O_2 \) and \( CO_2 \) fraction levels were monitored by Applied Electrochemistry gas analyzers (Amtek, Pittsburgh, PA). Inspired \( CO_2 \) fraction in the treadmill remained below 1.0%.

Protocol

Twenty-eight rats were divided equally into four groups of seven rats each: sedentary-normoxia, exercise-normoxia, sedentary-hypoxia, and exercise-hypoxia. On day 1, baseline recordings of \( T_b \) were obtained for 24 h during exposure to room air for all groups. On day 2, animals were exposed to either 24 h of hypoxia or 24 h of room air depending on the group. After day 2, after the animals had been in the treadmill for 48 h, the rats underwent euthanasia by decapitation, and brains and lungs were excised for histopathological study (see Histopathology).

The two exercise groups (normoxia and hypoxia) began walking at 10 m/min on the treadmill for 30-min intervals beginning at 0730 alternating with 30-min rest periods for the first 6 h of either hypoxia or room air exposure on day 2. Walking at 10 m/min is a mild level of exercise for the normoxic rat (12). After completion of the 6-h exercise period, the rats remained in the treadmill for an additional 18 h exposed to either hypoxia or room air. The two sedentary groups (normoxia, hypoxia) were studied also in the treadmill.

Histopathology

Rats underwent euthanasia by decapitation (with IACUC approval). After excision, brains and lungs were immersed in 10% formalin for a minimum of 24 h before sectioning. Tissues were embedded in paraffin and sectioned at 5-μm intervals for microscopic evaluation. Slides were stained with hematoxylin and eosin. Tissues were evaluated by a pathologist (P. T. Ostrow) blinded as to the source of the sections.

Coronal brain sections were evaluated for changes according to methods developed previously for a global brain ischemia model (15). The hippocampus in particular was studied because of its great sensitivity to hypoxia-ischemia and because its linear arrangement of neurons facilitates quantitative observation (15). Hypoxic neurons were identified by the presence of dark, pyknotic nuclei with loss of internal nuclear detail and/or shrunken eosinophilic cytoplasm (see Fig. 2A). The hippocampal formation and dentate gyrus were divided into seven segments by structural landmarks, and the percentage of cells exhibiting these changes was recorded in each segment as grades 1–4 (grade 1 = 1–10%, 2 = 11–50%, 3 = 51–75%, 4 = 76–100%) (15). Representative areas of deep gray matter, parietal cortex, and cerebellum from each brain were also evaluated for presence and severity of hypoxic neuronal changes.

Sections from each lung were stained with hematoxylin and eosin and evaluated also in blinded fashion for the presence of pulmonary capillary congestion (the entire capillary filled by a single line of contiguous erythrocytes or erythrocytes “side by side” within a capillary), intraluminal fluid (edema) or blood in alveoli or bronchioles, and collapse of airways. The sections were graded quantitatively from 1–4 for the presence of pulmonary capillary congestion and interstitial edema, intra-alveolar edema, intra-alveolar and/or bronchiolar bleeding, and collapse of airways. The total grade for the lungs included consideration of whether damage was judged to be focal or widespread.

Wet-Dry Ratios

Thirty-two additional rats were divided into four groups and studied according to the two normoxic and two hypoxic protocols described above. After completion of a protocol, the rats underwent euthanasia with pentobarbital sodium (100 mg/kg), and brains and lungs were excised quickly and
weighed. Subsequently, the tissues were dried at 70°C for 10–14 days until tissue weights were stable. Brain and lung wet-dry ratios were then calculated to estimate tissue water content (7, 31).

Statistical Analysis

T\(_b\) data were analyzed by using a two-way analysis of variance for repeated measures. If the F test was significant, the variance were tested post hoc by using a Bonferroni test. A P value of <0.05 was considered significant. Brain and lung histopathology and wet-dry data were analyzed by using Student’s unpaired t-test.

RESULTS

Normoxia

Figure 1 indicates T\(_b\) recordings from a sedentary normoxic rat and an exercising normoxic rat. Natural cycling of T\(_b\) was evident during the 24-h prehypoxic recording period in all rats. T\(_b\) rose during the dark period, as is characteristic for the nocturnal rat. In the sedentary normoxic rats on day 2, T\(_b\) fell to its normal nadir during the light period, followed by a second period of elevated T\(_b\) as the dark cycle ensued. By contrast, during the 6-h exercise period, the exercising normoxic rats showed cyclic elevations of T\(_b\) corresponding to each bout of walking (Fig. 1) such that the mean T\(_b\) for the exercise normoxic group was elevated significantly compared with the sedentary normoxic group as is shown in Table 1. After the exercise period,

<table>
<thead>
<tr>
<th>Group</th>
<th>T(_b) Normoxia, °C</th>
<th>T(_b) 6 h, °C</th>
<th>Nadir, °C</th>
<th>Time to Nadir, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>EH</td>
<td>37.61 ± 0.55</td>
<td>37.73 ± 1.25*</td>
<td>35.05 ± 1.69</td>
<td>10.51 ± 1.61*</td>
</tr>
<tr>
<td>SH</td>
<td>38.00 ± 0.36</td>
<td>36.15 ± 0.97†</td>
<td>35.03 ± 1.32</td>
<td>5.36 ± 1.83</td>
</tr>
<tr>
<td>EN</td>
<td>38.90 ± 0.95</td>
<td>39.65 ± 0.99†</td>
<td>38.29 ± 0.17</td>
<td>38.00 ± 0.99†</td>
</tr>
<tr>
<td>SN</td>
<td>38.29 ± 0.17</td>
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</tbody>
</table>

Values are means ± SD. EH, exercise-hypoxia; SH, sedentary-hypoxia; EN, exercise-normoxia; SN, sedentary-normoxia; T\(_b\) 6 h, mean body temperature (T\(_b\)) for first 6 h of experimental period on day 2. *P < 0.05 from SH; †P < 0.05 from SN.

T\(_b\) in the exercising normoxia group declined to values similar to those occurring in the sedentary normoxia group (Fig. 1).

Hypoxia

Figure 1 also indicates T\(_b\) recordings from a sedentary hypoxic rat and an exercising hypoxic rat. In the sedentary hypoxic rats the HTR led to a dramatic decline in T\(_b\) during the initial phase of exposure to hypoxia. Table 1 indicates that the mean T\(_b\) in the sedentary hypoxic group during hypoxia was reduced significantly relative to normoxia, with the nadir of the HTR being attained at ~5.5 h of hypoxia. By contrast, as is evident in Fig. 1, T\(_b\) began to decline with the onset of hypoxia in the exercising hypoxic rats, but the imposition of the serial bouts of walking abruptly counteracted this tendency for T\(_b\) to decline such that T\(_b\) was elevated in cyclic fashion with each bout of walking. Table 1 indicates that mean T\(_b\) for the exercising hypoxic group was not significantly different from either the prehypoxic T\(_b\) or the sedentary normoxic T\(_b\). However, the mean T\(_b\) for exercising hypoxic rats was significantly less than that of the exercising normoxic animals. After cessation of the exercise period, T\(_b\) declined rapidly toward nadirs similar to those attained in the sedentary hypoxic group. The nadir values for the sedentary hypoxic and exercising hypoxic groups were not significantly different. However, the time for T\(_b\) to reach its nadir was more than twice as long in the exercising hypoxic group compared with the sedentary hypoxic group (Table 1).

Histopathology

Brain. On neuropathological examination, the exercising hypoxic group of rats exhibited significantly greater brain damage compared with either the sedentary hypoxic group or the normoxic groups. Examination of the hippocampus in exercising hypoxic rats consistently revealed widespread near grade 4 (most severe) damage in the form of shrunken eosinophilic cells and pyknotic nuclei, particularly in the dentate nucleus. These cytological features are illustrated in Fig. 2, which shows photomicrographs of coronal sections through the hippocampus of a normoxic sedentary rat with sections from the hippocampus of a rat exercised in hypoxia. In addition, examination of the cerebellum (not shown) in the exercising hypoxic group

![Fig. 1. Telemetry recordings of body temperature (T\(_b\)) from a sedentary normoxic rat and an exercising normoxic rat. Natural cycling of T\(_b\) was evident during the 24-h prehypoxic recording period in all rats. T\(_b\) rose during the dark period, as is characteristic for the nocturnal rat.](http://jap.physiology.org/DownloadedFrom/10.1152/jappl.00021.2003)
revealed many missing or shrunken Purkinje cells with entire zones of missing cells in some regions. A cleft separating the molecular and Purkinje cell layers from the granule cell layer, i.e., a lamina dessicans, typical of hypoxic injury, was observed in the cerebellum of many animals. Table 2 indicates that brain damage was significantly higher in the sedentary hypoxic group compared with the normoxic groups. Therefore, although exercise in hypoxia caused the greatest brain damage of any condition, hypoxia alone in the sedentary rats caused significantly greater brain damage than either normoxia or exercise in normoxia.

Table 2. Histopathology grading for brains and lungs

<table>
<thead>
<tr>
<th></th>
<th>Brains</th>
<th>Lungs</th>
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<tbody>
<tr>
<td>SN</td>
<td>1.00 ± 0.15</td>
<td>1.00 ± 0.13</td>
</tr>
<tr>
<td>EN</td>
<td>1.00 ± 0.14</td>
<td>2.00 ± 0.14</td>
</tr>
<tr>
<td>SH</td>
<td>1.63 ± 0.18*</td>
<td>1.75 ± 0.17</td>
</tr>
<tr>
<td>EH</td>
<td>3.64 ± 0.25†</td>
<td>3.71 ± 0.26‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05, †P < 0.01 relative to SN, ‡P < 0.05 relative to SH, based on a grading scale in which 1.0 = little or damage vs. 4.0 = severe damage by blinded pathology examination.
Table 3. Brain and lung wet-dry ratios

<table>
<thead>
<tr>
<th></th>
<th>Brain</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>EN 4.457(0.155)</td>
<td>SN4.408(0.057)</td>
<td>EH4.440(0.111)</td>
</tr>
<tr>
<td>SN 4.408(0.057)</td>
<td>SH4.381(0.069)</td>
<td>SH4.381(0.069)</td>
</tr>
<tr>
<td>diff 0.049 ns</td>
<td>-0.027 ns</td>
<td>0.059 P &lt; 0.05</td>
</tr>
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<tbody>
<tr>
<td>SN 4.659(0.283)</td>
<td>SN4.659(0.283)</td>
<td>EH4.490(0.249)</td>
</tr>
<tr>
<td>EN 4.286(0.342)</td>
<td>SH4.121(0.784)</td>
<td>SH4.121(0.784)</td>
</tr>
<tr>
<td>diff 0.373</td>
<td>0.353 P &lt; 0.05</td>
<td>0.369 P &lt; 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SD; SN (n = 6), EN (n = 8), SH (n = 8), EH (n = 10). diff, Difference; ns, not significant.

Lungs. As with the brain, the lungs from the exercising hypoxic group displayed widespread damage near grade 4 (most severe) as evidenced by pulmonary capillary congestion, large areas of collapse, intra-alveolar and interstitial edema, and intra-alveolar bleeding with bronchiolar bleeding in some instances. These cytological features are illustrated in Fig. 2, which shows photomicrographs of sections of pulmonary tissue obtained from a sedentary normoxic animal and sections of lung obtained from a rat exercised in hypoxia. Table 2 indicates that increases in gradation of lung damage were recorded for both the exercising normoxic group and the sedentary hypoxic group. However, these increases in gradation of damage did not prove to be significant.

Wet-dry ratios. Table 3 indicates that neither exercise in normoxia nor sedentary hypoxia altered brain water significantly. However, the rats exercising in hypoxia had significantly elevated brain water compared with the rats that remained sedentary in hypoxia. For the lungs, both exercise in normoxia and sedentary hypoxia reduced water content significantly. By contrast, the rats exercising in hypoxia had significantly increased lung water content compared with the rats that remained sedentary in hypoxia. Therefore, exercise in hypoxia was associated with significantly increases in water content of both brains and lungs.

DISCUSSION

The present results indicate that imposition of an exercise challenge at the onset of a sustained period of exposure to normobaric hypoxic delays, but does not prevent, the HTR in Sprague-Dawley rats at an ambient temperature of 25°C. The serial bouts of walking during the initial 6 h of hypoxia caused cyclic elevations in T\textsubscript{b} that served to counteract the natural tendency for T\textsubscript{b} to decline during this period as observed in the sedentary hypoxic rats. However, an HTR was likely present in the rats during the exercise period in hypoxia because the mean T\textsubscript{b} in this group failed to rise, in contrast to the rats exercising in normoxia, in which T\textsubscript{b} rose significantly above both prehypoxic and sedentary normoxic levels. After cessation of exercise, as hypoxia continued, T\textsubscript{b} declined to reach a nadir that was not significantly different from that attained in the sedentary hypoxic rats. However, it took twice as long for the exercising hypoxic rats to reach their T\textsubscript{b} nadir compared with the sedentary hypoxic rats. The exercise-induced counteraction of the HTR during the initial 6 h of hypoxia was associated with significant increases in brain and lung damage and brain and lung water contents compared with sedentary rats during hypoxia. These observations support the hypothesis that the HTR serves to protect brain and lung during hypoxia.

Interpretation of the present observations must be qualified by the recognition that the physiological responses to both hypoxia and exercise are complex. Moreover, the mechanisms responsible for the HTR are unclear (10, 23, 27). The HTR involves both a decline in heat production and an increase in heat loss, likely due to a central resetting of the thermoregulatory set point (10, 27) leading to the HTR, a regulated decline of T\textsubscript{b} (14). The exercise stimulus and the HTR stimulus appear to be algebraically additive such that when they occur simultaneously there is no significant alteration in T\textsubscript{b}, at least at these levels of hypoxia and exercise. Thus the HTR stimulus seems to persist throughout the exercise period, and when exercise terminates, the HTR becomes fully manifest with T\textsubscript{b} declining to values similar to those displayed by sedentary hypoxic animals. Hence, once a command is initiated via a hypoxic stimulus to reset the thermoregulatory set point, physiological systems are set in motion that persist in driving T\textsubscript{b} toward the new set point or nadir of the HTR in the face of important offsetting stimuli, such as those associated with muscular exercise.

Although multiple central nervous and peripheral interactions are possible given the complexities of the exercise response and the HTR, it seems likely that the primary mechanism that accounts for the ability of exercise to offset the HTR is an increase in muscle heat production due to increased O\textsubscript{2} demand. Although we did not measure O\textsubscript{2} uptake (V\textsubscript{O\textsubscript{2}}) directly, changes in T\textsubscript{b} may be taken to reflect changes in V\textsubscript{O\textsubscript{2}}. Thus, during exercise in hypoxia, there is likely a higher V\textsubscript{O\textsubscript{2}} leading to a higher T\textsubscript{b} for a given level of inspired O\textsubscript{2}. Although we did not measure arterial blood gases in this study, previous work by Gonzalez et al. (12) indicates that the arterial PO\textsubscript{2} level is not lower in rats exercising in hypoxia compared with rats exposed to hypoxia alone owing to the high pulmonary diffusing capacity of the rat. Although it may be that systemic delivery of O\textsubscript{2} is not reduced in exercising animals exposed to hypoxia compared with hypoxia alone, further experiments are necessary to determine more specifically how much tissue PO\textsubscript{2} actually declines under the conditions of this study. Although we did not measure maximal or peak V\textsubscript{O\textsubscript{2}}, our observations suggest that intermittent mild exercise for 6 h in hypoxia was close to the maximal effort for these rats. Attempts to continue the exercise protocol beyond 6 h in hypoxia were associated with the rats resisting continuation of walking. Thus, although the rats exercised during the HTR, their functional performance appeared to be limited compared with normoxic rats. We have shown that locomotor activity in nonexercising rats is impaired significantly.
during the HTR (3, 4), and this factor may have contributed to the reduction of their functional performance in addition to hypoxia per se.

Histopathological examination revealed significantly greater damage in brain and lungs in rats studied 18 h after the 6-h hypoxic exercise protocol compared with the sedentary hypoxic rats or the normoxic rats. In addition, comparison of wet-dry ratios in four separate groups of rats indicates that water contents were elevated significantly in the brains and lungs of the exercising hypoxic rats compared with the sedentary hypoxic rats. The percentage increase in brain water content in the exercising hypoxic rats (+1.35%) was somewhat greater than the percentage increase in brain water content that we observed in previous studies of sheep displaying elevated intracranial pressure and AMS-HACE (+1%) (7, 31). The brain extracellular space is small so that small increments in water content elicit large increments in intracranial pressure (17). The increased brain water content observed in our exercising hypoxic rats is similar in magnitude to that reported in other studies of experimental production of brain edema in the rat (8). Severe damage was observed in the hippocampus and cerebellum, suggesting that these lesions may be associated with impairment of learning and memory as well as locomotor difficulties. Severe pulmonary damage was present, as indicated by pulmonary capillary congestion, intra-alveolar hemorrhage, and interstitial and intra-alveolar edema. The pulmonary lesions suggest that impairment of arterial oxygenation may persist after return to normoxia after hypoxic exercise in this setting.

The cellular and molecular mechanisms mediating the hypoxic brain and lung damage are uncertain, but data from Wood et al. (29) suggest that reactive O2 and nitrogen species are likely to play a major role in mediating hypoxic tissue damage although other mediators probably play a role as well (30). Mark and Davis (21) have demonstrated that hypoxia increases cerebral microvascular paracellular permeability. It is possible that, in addition to lowering tissue PO2 levels, exercise may augment the latter hypoxic inflammatory and permeability responses. In the present study, the exercise period was confined to the first 6 h of hypoxia, when the HTR would be occurring naturally. The subsequent delayed manifestation of the HTR after cessation of exercise did not appear to provide protection. Further studies are required to determine whether brain and lung damage would occur if exercise is imposed later in hypoxia after resolution of the HTR.

Roach et al. (26) have demonstrated that exercise imposed after the onset of hypoxia exacerbates symptoms of AMS in humans. AMS is considered to be a benign form of HACE, and AMS can evolve into lethal HACE and/or HAPE (16, 18). In this regard, our present observations lend strong support to the hypothesis that exercise early in hypoxia can be deleterious to both humans and animals. The brain and lung lesions and increased tissue water contents we observed in our exercising hypoxic rats resemble HACE and HAPE, respectively, as described in humans. The mechanisms mediating HACE and HAPE in humans remain uncertain. In humans, HACE is associated with learning and memory problems as well as ataxia (6, 16). These cognitive and motor disturbances are compatible with the hippocampal and cerebellar lesions we observed in our rats. HAPE in humans is a high-permeability type of edema with rupture of the blood-gas barrier and intra-alveolar hemorrhage (1). These responses are similar to the intra-alveolar edema and hemorrhage we observed in our rats. Because the brain and lung lesions elicited by exercising the hypoxic rat resemble human HACE and HAPE, respectively, it seems likely that hypoxic exercise in the rat may prove to be a useful animal model for the investigation of the mechanisms that mediate AMS, HACE, and HAPE. Moreover, hypoxic exercise appears to be a method for inducing reproducible brain and lung damage in the absence of ischemia.

Ginsberg et al. (11) have demonstrated that brain damage after ischemia is reduced in the presence of brain cooling. In addition, clinical studies support the view that neurological damage after cardiac arrest or stroke is reduced significantly in patients with induced hypothermia (2). Our experiments emphasize the fact that a higher Tb during hypoxia is associated with tissue damage and that a regulated decline in Tb during the HTR in the rat is protective. Because the HTR is an allometric function of body mass, it is unlikely that adult humans exhibit the HTR, although high altitude or hypoxia reduces both nonshivering and shivering thermogenesis in adult humans and small mammals (5, 10, 23, 27). Thus periodic bouts of exercise early in hypoxia in humans before full respiratory acclimatization (26) may raise Tb to a level that increases the propensity for hypoxic tissue damage in susceptible organs.

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