Circadian rhythms of body temperature and activity levels during 63 h of hypoxia in the rat

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Bishop, B., G. Silva, J. Krasney, A. Salloum, A. Roberts, H. Nakano, D. Shucard, D. Rifkin, and G. Farkas. Circadian rhythms of body temperature and activity levels during 63 h of hypoxia in the rat. Am J Physiol Regulatory Integrative Comp Physiol 279: R1378–R1385, 2000.—The hypothermic response of rats to only brief (~2 h) hypoxia has been described previously. The present study analyzes the hypothermic response in rats, as well as level of activity (La), to prolonged (63 h) hypoxia at rat thermoneutral temperature (29°C). Mini Mitter transmitters were implanted in the abdomens of 10 adult Sprague-Dawley rats to continuously record body temperature (Tb) and La. After habituation for 7 days to 29°C and 12:12-h dark-light cycles, 48 h of baseline data were acquired from six control and four experimental rats. The mean Tb for the group oscillated from a nocturnal peak of 38.4 ± 0.18°C (SD) to a diurnal nadir of 36.7 ± 0.15°C. Then the experimental group was switched to 10% O2 in N2. The immediate Tb response, phase I, was a disappearance of circadian rhythm and a fall in Tb to 36.3 ± 0.52°C. In phase II, Tb increased to a peak of 38.7 ± 0.64°C. In phase III, Tb gradually decreased. At reoxygenation at the end of the hypoxic period, phase IV, Tb increased 1.1 ± 0.25°C. Before hypoxia, La decreased 70% from its nocturnal peak to its diurnal nadir and was entrained with Tb. With hypoxia La decreased in phase I to a level of activity (La) well below the reported thermoneutral zone of the rat (29–31°C) (14). The low Ta clearly could influence the parameters of the hypoxic response (32). Thus our intent was to characterize the full hypoxic effect on the circadian rhythms of body temperature (Tb) and level of activity (La) in rats maintained at 29°C. The experimental group was switched to 10% O2 in N2. The immediate Tb response, phase I, was a disappearance of circadian rhythm and a fall in Tb to 36.3 ± 0.52°C. In phase II, Tb increased to a peak of 38.7 ± 0.64°C. In phase III, Tb gradually decreased. At reoxygenation at the end of the hypoxic period, phase IV, Tb increased 1.1 ± 0.25°C. Before hypoxia, La decreased 70% from its nocturnal peak to its diurnal nadir and was entrained with Tb. With hypoxia La decreased in phase I to a level of activity (La) well below the reported thermoneutral zone of the rat (29–31°C) (14). The low Ta clearly could influence the parameters of the hypoxic response (32). Thus our intent was to characterize the full hypoxic effect on the circadian rhythms of body temperature (Tb) and level of activity (La) in rats maintained at 29°C. The lower limit of the thermoneutral zone for rats (14). The rats were habituated and acclimated to the 29°C Ta (34), and then the circadian patterns of Tb and La of the rats were recorded and analyzed for 48 h before, during, and 48 h after exposure to an inspired gas mixture of 1% O2 in N2. Tb normally oscillates in phase with dark-light cycles. The circadian rhythm of Tb depends on whether an animal is nocturnal or diurnal. In the nocturnal rat Tb has its peak during the night (the dark cycle) and its nadir in the day (light cycle) (33). The La of the rat also shows a circadian rhythm that is time-locked to an imposed 12:12-h dark-light cycle.

After our study was submitted for publication, Mortola and Seifert (23) published results of a similar study in which rats were subjected to 10.5% O2 for 7 days but without specifying Ta. They found, as have we,
that the hypoxia-induced hypothermia did not persist but reversed and climbed. As will be shown, the amplitude of the rise in $T_b$ at an $T_a$ of 29°C is inconsistent with the results reported in the paper by Mortola and Seifert (23).

**METHODS**

**Animals**

This study was reviewed and approved by the University at Buffalo Institutional Animal Care and Use Committee. Ten adult male Harlan Sprague-Dawley rats, with body weights ranging from 268 to 497 g, were studied. Before the experiments, a sterile Mini Mitter probe (diameter 10 mm) for detecting $T_b$ and $L_a$ was implanted under aseptic conditions in the abdominal cavity of each rat under pentobarbital sodium anesthesia (40 mg/kg ip). On recovery from surgery each rat was weighed and then placed in its own cage in an all-weather room. All animals were exposed to identical baseline conditions. Four of the animals were selected at random to be included in the experimental hypoxia group.

**Experimental Conditions**

The all-weather room was soundproof and equipped with automated systems that permitted tight control of $T_a$ and lighting cycles over a prolonged period of time. In the present experiment $T_a$ was set at 29°C and the lighting cycle was set at a 12:12-h dark-light cycle, switching at 0600 and 1800.

**Data Detection**

Each cage was placed on a receiver for the temperature and activity signals transmitted by the implanted probe. Cages housing the hypoxic rats resided within a large plastic chamber through which either room air or a 10% $O_2$ in $N_2$ gas mixture was delivered at a flow rate of 5 l/min (Fig. 1). Additional cages for the control rats were placed on top of the plastic chamber, each over a Mini Mitter receiver identical to those under the cages of the hypoxic group. Each animal was fed ad libitum and left untethered and undisturbed throughout the 159 h of the experiment.

**Creating the Hypoxic Environment**

To induce normobaric hypoxia, a nitrogen flood valve was opened initially for purposes of rapid induction. As the $O_2$ concentration in the chamber approached 10%, preset valves were opened to maintain a continuous hypoxic (10% $O_2$) mixture in the chamber. The reduction of chamber gas to the 10% $O_2$ level required 35–40 min and was always initiated at 1700 when $T_b$ and $L_a$ were rising in their circadian cycles. Chamber $CO_2$ concentration was always $<0.1%$. After 63-h exposure to the hypoxic gas all the valves were closed, and the chamber was unsealed, making reoxygenation essentially instantaneous. The afternoon after reoxygenation, each rat was again weighed.

**Data Acquisition and Reduction**

The Mini Mitter telemetry system permitted collection of continuous data for the entire 159 h of the experiment. The temperature-specific frequency and the instantaneous position of an animal were transmitted through a multiplexer and relayed to a computer in an adjacent room. A Windows-based software program (VitalView, Mini Mitter) converted the frequency of the probe to temperature. The probes were calibrated both before implantation and at the end of an experiment. All recorded changes in $T_b$ were expressed in degrees centigrade, and each change in the position of an animal was expressed as a “count” of activity. Results for both parameters were tabulated every 15 min. These telemetry signals were converted to an ASCII file format and entered into the Microsoft Excel Workbook file format. Graphs of $T_b$ and $L_a$ over the duration of an experiment (159 h) were generated for each animal.

**Data Analysis**

Data from animals in each group (i.e., the control and hypoxic groups) were pooled, when appropriate, and analyzed for a variety of variables, including the averages and magnitudes of circadian rhythms, the diurnal nadirs, the nocturnal peaks, and rise and decay times.

**RESULTS**

**Effects of hypoxia on body weight.** In Table 1 the mean body weights for the control and experimental hypoxic groups before and at the end of the experiment are listed. After 63-h exposure to 10% $O_2$, the hypoxic group lost $>40$ g or about 10% of their body mass. In contrast, none of the controls lost weight, and some gained about 10 g over the 159 h.
Prehypoxic circadian rhythms of $T_b$ and $L_a$. As exemplified by the traces from a single animal in Fig. 2, $T_b$ and $L_a$ oscillated in phase with the dark-light cycles in the control rats. $T_b$ oscillated about 1°C around the mean of 37.0°C with the peak at 38.1°C during the dark cycle and the mean nadir of 37.1°C during the light cycle. These rhythms persisted in every control rat throughout the entire experiment. The magnitudes of these oscillations were not different from the base-line data recorded in the prehypoxic period from the hypoxic rats. All $T_b$ prehypoxic traces were superimposable.

Body Temperature Responses To Hypoxia

$T_b$ before 10% $O_2$. The oscillations in $T_b$ for the control animals, as shown by the representative plot in Fig. 2, peaked at a group average of 38.4 ± 0.18°C (SD) during the dark cycle and decreased to an average nadir of 36.7 ± 0.15°C during the light cycle.

Changes in $T_b$ during 10% $O_2$. At the onset of hypoxia $T_b$ decreased dramatically in each of the four rats (Fig. 3). This hypothermic component of the hypoxia-induced response was similar in magnitude, direction, and pattern in all animals. For convenience of analysis we defined four well-demarcated components or phases in $T_b$ response to hypoxia (Fig. 4). Phase I was from onset of hypoxia to $T_b$ nadir. Phase II spanned the elevation of $T_b$ from the nadir to the hyperthermic peak. Phase III included the decline in $T_b$ from the hyperthermic peak to the end of the hypoxia. Phase IV occurred with the termination of hypoxia.

Table 1. Mean body weights for control and hypoxic groups of adult Sprague-Dawley rats at beginning and end of 159-h experiment conducted at 29°C

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Initial Wt, g</th>
<th>Final Wt, g</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>6</td>
<td>381.2 ± 38.2</td>
<td>390.8 ± 31.7</td>
<td>+3%</td>
</tr>
<tr>
<td>Hypoxics</td>
<td>4</td>
<td>403.1 ± 32.5</td>
<td>361.6 ± 31.6</td>
<td>-10%</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$ = no. of rats. Hypoxic group was exposed to 63 h of 10% $O_2$.

Phase I, the hypothermic component of the response. The mean $T_b$ values for the hypoxic group are plotted along with the mean $T_b$ values for the control group in Fig. 4. With the onset of hypoxia not only was the $T_b$ circadian rhythm totally abolished, but $T_b$, which had been rising toward its normal nocturnal peak at the onset of hypoxia, reversed and fell 1.17 ± 0.25°C at an average rate of 0.50 ± 0.34°C/h (SD) to reach a nadir over the next 3.5 ± 0.68 h. This decrease carried $T_b$ to a temperature significantly below its normal diurnal nadir. At the same point in time, $T_b$ for the control group increased by an average of 0.95 ± 0.19°C to its peak of 37.8°C. Figure 4 shows that the average $T_b$ for the hypoxic group decreased to a minimum of 36.29 ± 0.52°C from its initial value of 37.42 ± 0.31°C. This initial decline in $T_b$, comprising phase I of the response, has been reported previously for small mammals (9).

Phase II, the hyperthermic component of the response. $T_b$, after reaching its hypothermic nadir, reversed and over the next 24 h rose 2.4°C at a rate of 0.10 ± 0.04°C/h to a peak of 38.7 ± 0.3°C. This $T_b$ peak significantly exceeded the normal prehypoxic noctur-
Hypoxia abolishes rat temperature and activity rhythms

Circadian rhythm of $L_a$ before 10% $O_2$. Before hypoxia, $L_a$ oscillated in phase with the dark-light cycles (control data in Fig. 2, and the prehypoxic data in Fig. 5A). As would be expected in a nocturnal animal, the $L_a$ oscillations reached a peak of $\sim 50$ counts/15 min during the dark cycle and a nadir of $\sim 7$ counts/15 min during the light cycle. The absolute $L_a$ varied among animals. Nonetheless, the periods of the average $L_a$ cycles were not different from those for either $T_b$ or the dark-light cycles.

Changes in $L_a$ during 10% $O_2$. $L_a$, which was rising at the time the hypoxia was imposed, changed dramatically with the onset of hypoxia as shown in Fig. 5B and the bottom trace of Fig. 6. The circadian rhythm of $L_a$ was totally disrupted, and $L_a$ gradually fell toward silence as $T_b$ declined in phase I. Within 7 h of the onset of hypoxia (i.e., during phase I of the $T_b$ response) $L_a$ counts had decreased from their nocturnal peak of 50 counts/15 min to 7 counts/15 min. By the time $T_b$ reached its hypoxic nadir, $L_a$ became essentially quiescent despite the fact that the dark cycle was still in progress. $L_a$ remained significantly depressed throughout $T_b$ phase II response. In fact, it was during this phase that $L_a$ was most depressed by the hypoxia. During phase II of the $T_b$ response, the activity counts for the hypoxic rats remained near zero, well below those of the control group. About 25 h after the onset of hypoxia, at the onset of phase III when $T_b$ was falling, $L_a$ increased somewhat, but remained well below that of the prehypoxic phase I period or the $L_a$ of the control group.

$L_a$ gradually increased and displayed low-amplitude oscillations (25 vs. 15 counts/15 min) compared with the recordings in the prehypoxic period or those of the control group (50 vs. 7 counts/15 min).

Reoxygenation. In phase IV (and over the first 10 h after reoxygenation) the amplitude and period of the $L_a$ circadian rhythm were fully restored to their normal prehypoxic values (Figs. 5B and 6).

Discussion

Hypoxia-induced weight loss. The weight gain of the control group and the weight loss of the hypoxic group over the 159 h of the experiment (Table 1) support the concept that hypoxia has important effects on metabolism (10, 26). Sustained hypoxia reduces oxygen consumption by 56% (23).

Circadian rhythms. The Sprague-Dawley rats in this study were acclimated and maintained at their thermal neutral temperature of 29°C and habituated to 12:12-h dark-light cycles. These oscillations, obtained at 29°C, are not different from those reported in other studies in which no mention is made of the $T_a$ (14, 23). The fact that $T_b$ is tightly entrained to the imposed 12:12-h dark-light cycle, regardless of $T_a$, is evidence that the circadian timing system tightly controls the thermal regulatory machinery independently of $T_a$.

$L_a$ also oscillated in phase with the dark-light cycles. As would be expected in the nocturnal rat, $L_a$ peaked during the dark cycle and decreased to a nadir (near zero) during the light cycle (Fig. 5), confirming the recent findings of Mortola and Seifert (23). $L_a$ was more variable on a moment-to-moment basis than $T_b$. How-
ever, the moving averages of Lₐ across the dark-light cycles were relatively reproducible.

Effects of hypoxia on the circadian rhythms. With the onset of hypoxia the circadian rhythms of both Tₜ and Lₐ were abolished for the entire 63-h hypoxic exposure (Fig. 6). Hypoxia affected Tₜ and Lₐ differently. The Tₜ response to hypoxia was multiphasic, whereas Lₐ was totally suppressed initially and then returned but remained at a low level devoid of circadian rhythm for the duration of the hypoxia. These differences provide...
evidence that $T_b$ and $L_a$, although interrelated through metabolic mechanisms (31), do not have obligatory linkages.

**Phase I of the hypoxia-induced $T_b$ response.** The abrupt fall in $T_b$ after the onset of hypoxia was striking and suggested an immediate activation of mechanisms designed to drive core temperature to a critical value that is optimum for maintaining a suitable balance of oxygen supply vs. demand (25). This hypoxia-induced hypothermia (phase I, Fig. 5) was not unexpected. Many species of small animals, along with human infants, lower their $T_b$ when exposed to hypoxia (1, 9, 35). This fall in $T_b$ and the accompanying fall in metabolism (10) are considered to have survival advantage (36). It has been proposed that this hypoxia-induced hypothermia may confer protection on certain organs, particularly the brain (36). Small changes in brain temperature during hypoxia have a marked influence on the magnitude of cellular damage (13).

**Phases II and III of the hypoxia-induced $T_b$ response.** Before the Mortola and Seifert (23) study we had not expected either the transiency of the hypothermic component (phase II) of the $T_b$ response to prolonged hypoxia nor the subsequent hyperthermia. In their rats (23) the hypoxia-induced hypothermia never rose above the nadir of the prehypoxic oscillations. In other words, the $T_b$ in their rats failed to reach the normal nocturnal $T_b$, let alone a hyperthermic $T_b$. In fact, only after hypoxia was terminated did the peak $T_b$ rise to its normal nocturnal level in their rats. Both their study and ours used Sprague-Dawley rats and a sustained exposure to ~10% inspired $O_2$. A likely difference between the protocols in the two studies was the $T_a$. Unfortunately, Mortola and Seifert (23) did not report the $T_a$ at which their study was performed. Our rats were acclimated and maintained at 29°C for the entire study. This thermoneutral temperature was selected for the express purpose of minimizing the need of the rats to initiate thermoregulatory responses. We now know, based on unpublished results obtained in our laboratory, that $T_a$ strongly influences each phase of the hypoxia-induced response of $T_b$ and $L_a$, thereby accounting for the differences between our results and those of Mortola and Seifert (23).

**Potential Mechanisms Underlying the Hypothermia of the Hypoxia-Induced Responses**

Mechanisms inducing the hypothermia remain to be determined. For hypothermia to occur, heat loss must exceed heat production (15). This imbalance could be achieved by decreasing heat production, by increasing heat loss, or by both. In the rat, the tail serves as a major thermoregulatory organ (30). In an $T_a$ below the thermoneutral range, the tail is maximally constricted (14, 30). In warm environments vasodilation of tail vessels is a major way a rat loses heat. Another is by grooming the pelt with saliva, which accelerates evaporative heat loss. In rats acclimated to prolonged heat stress the parotid saliva glands undergo excessive growth (14). In the dog, hypoxia acts peripherally on the oxygen-sensitive receptors in the carotid body to evoke reflex noncholinergic cutaneous vasodilation (2), and systemic hypoxia causes cutaneous vasodilation (4).

Hypoxia is thought to act centrally at innumerable sites. These include the circadian pacemaker in the suprachiasmatic nucleus (SCN) (6), the thermosensitive neurons in the thermoregulatory areas of the anterior and posterior hypothalamus (5, 21), the pontine and medullary neurons involved in respiratory and cardiovascular control (10), and the raphe nuclei and other brain regions involved in sleep states. It remains to be determined what the exact roles of any of these brain regions, or the central or peripheral chemoreceptors (10, 19), play in the hypoxia-induced hypothermia or the subsequent hyperthermia.

**Potential Mechanisms Underlying Hyperthermia of Hypoxic-Induced Responses**

Acute hypoxia stimulates an increase in dry heat loss in the rat (15). The heat loss response is markedly affected by $T_a$. At 22°C, the increase in heat loss is robust; however, at 30°C, there is a modest rise in heat loss and then a decrease with continued hypoxia. At 32°C, hypoxia causes a decrease in dry heat loss. This reduction in the heat loss response with rising $T_a$ may explain the hyperthermic response of hypoxia observed in this study.

**Potential Mechanisms for Hypoxia-Induced Changes In $L_a$**

The underlying mechanisms for the sustained suppression of $L_a$ with the onset and duration of the sustained hypoxia are not known. It seems highly unlikely that $L_a$ was suppressed to minimize heat production because $L_a$ suppression was greatest when $T_b$ was climbing to its hyperthermic peak (phase II) and was least when $T_b$ was falling during phase III. For the same reason, it is unlikely that the suppression of $L_a$ is a nonspecific response occurring secondary to the changes in $T_b$ (31). Perhaps some as yet unidentified centrally driven suppression of motor systems is activated by hypoxia. Hypoxia is known to depress shivering, nonshivering, and behavioral thermogenesis by decreasing the set point for thermogenesis (10, 23).

In humans, an acute exposure to hypoxia results in nausea and vomiting and a general malaise (17). Rats do not vomit, but their sudden and sustained decrease in activity in response to hypoxia could be a reflection of a malaise induced by the hypoxic environment. It may be that $L_a$ could serve as a general indicator of the level of “acute altitude illness” experienced by the rat along with reduced food and water intake (17).

During hypoxia endogenous opioids are elevated (16) and may contribute to a decline in the $T_b$ set point (22). Arginine vasopressin is upregulated, and this response has been postulated to contribute to the hypoxic response (36). However, Brattleboro rats, which lack arginine vasopressin, display a prominent hypoxic response (5). Histamine is released centrally during hyp-
Hypoxia (8), and infusions of histamine into the fourth ventricle induce hypothermia (7). Other substances with thermic properties are lactate (29), adenosine, and endogenous opioids (11).

Several studies support a role for nitric oxide in the hypoxic response (12). Maskrey (20) reported that clamping \( T_b \) during hypoxia by means of abdominal heating coils fails to prevent the decline in metabolic rate. This observation and other evidence suggest that the hypothermia is in large part secondary to a primary decline in metabolic rate (10).

In addition, systems that suppress heat production could be turned off, leading to a rapid increase of metabolic rate. It is well established that arterial hypoxia elevates circulating levels of catecholamines (17), and elevated catecholamines could certainly account for the onset of cutaneous vasoconstriction and increased heat production. In this context, it is an intriguing physiological paradox that the rat is able to display the hypoxic response in the face of such intense catecholaminergic activity. It may be that the systems that drive hyperthermia are activated early in hypoxia but their effects do not become manifest until later when the opposing systems that drive hypothermia withdraw. On the other hand, activation of the hyperthermic systems may be delayed until the hypothermic drives are turned off. Are the systems that drive hypothermia actively turned off or are they fatigued? Is there early hypoxic suppression of catecholamine synthesis and/or release from adrenergic neurons and chromaffin tissue that is then relieved by later increases in tissue oxygen delivery owing to acclimation? Further experimental studies are required to resolve these important questions. Although it may be that the body perceives that continuing the hypoxic response is incompatible with homeostasis, one might predict that the removal of the protective benefits of the hypoxic response and the onset of hyperthermia-hypermetabolism would be devastating physiologically. In this regard, we have reported in preliminary form that rats maintained at an \( T_a \) of 29°C during sustained hypoxia suffer significantly greater brain damage than rats maintained at 25 or 21°C (18).

Hypoxic Suppression of Circadian Rhythms

Hypoxia elicited important disturbances of circadian rhythms for both \( T_b \) and \( L_a \). This observation confirms the previous study of Poncet et al. (28) who reported that hypoxia disturbs daily rhythms of central neurotransmitters and the most recent report of Mortola and Siefert (23). The response patterns of \( T_b \) in our study were independent of the response patterns of \( L_a \). \( L_a \) remained suppressed even though \( T_b \) rose rapidly in phase II (Fig. 6). Hypoxia could either affect directly the output of the circadian pacemaker in the SCN (6) or the response of the SCN to the zeitgebers; however, no specific data are available on this point. It is also probable that hypoxia interferes at some point(s) along the effector pathways from the SCN to thermoregulatory and motor control centers. These influences may be due to the direct effects of hypoxia, due to mediators released by hypoxia, or due to input from specific reflexes such as those evoked by the arterial chemoreceptors. Mortola and Siefert (23) postulated that hypoxia more likely influences hypothalamic thermoregulatory centers as opposed to the SCN because a reduction in the amplitude of the \( T_b \) rhythm appeared later in their hypoxic exposure. However, this notion requires further experimental support as the restoration of the rhythm could have simply represented partial relief of hypoxia due to respiratory acclimatization. In any case, the abolition of circadian patterns by reduced oxygenation has profound implications for maintaining important physiological functions such as sleep (27) and intake of food and water. These functions are clearly disturbed in this situation (17). Moreover, it is uncertain as to how long these disturbed circadian patterns would persist if hypoxia were continued beyond 63 h. Further studies are required to explore this question.

In summary, this study has revealed that when adult rats are exposed for 63 h to a sustained 10% \( O_2 \) in a 29°C environment, they initially drop their \( T_b \), depress their \( L_a \), and lose their circadian rhythms for both variables. When hypoxia is extended past 2 h, the initial hypothermia (phase I) is followed first by a relative hyperthermia (phase II) and then a gradual return toward a “normal” \( T_b \) (phase III). This hyperthermic component of the \( T_b \) response to prolonged hypoxia has not been reported previously. The \( T_a \) of 29°C is the likely cause. Putative physiological mechanisms are considered to account for each event in this multifaceted response to prolonged hypoxia.

Perspectives

Hypoxia is a common stimulus encountered whenever one experiences sleep apnea, climbs mountains, or suffers a pulmonary disease. Hypoxia has long been recognized as a powerful stimulus that evokes responses in numerous physiological and biochemical regulatory systems including those controlling the circadian rhythms of \( T_b \) and \( L_a \), respiration, circulation, thermogenesis, metabolism, and erythropoiesis. The importance of this study is the demonstration that hypoxia, when introduced in a thermoneutral environment of 29°C, immediately disrupts the circadian rhythms of \( T_b \) and \( L_a \), causes a severe depression of \( L_a \), and evokes a complex three-component response in \( T_b \). On reoxygenation the circadian rhythms of \( T_b \) and \( L_a \) immediately reappear. The challenge for the future is the identification of the physiological, biochemical, and molecular mechanisms by which hypoxia causes these widespread and drastic effects.

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REFERENCES


