Role of chemoreception in cardiorespiratory acclimatization to, and deacclimatization from, hypoxia

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During sojourn to hypoxia of high altitudes, a progressive time-dependent hyperventilation occurs over the initial several days of sojourn. On return to sea level normoxia, the hyperventilation persists, slowly returning to presojourn levels (Fig. 1). This time-dependent ventilatory acclimatization and deacclimatization also occurs during all sleep states (7) and is slightly more pronounced during exercise (24). These features are also present in several mammals, including the rat, goat, and pony, although these species complete ventilatory acclimatization in a shorter time period than humans, who continue to increase the intensity of hyperventilation even over 10–15 days or more (11, 23, 60). Note in Fig. 1 that arterial Po2 (PaO2) increases substantially as ventilatory acclimatization proceeds, which means, by definition, that the ventilatory response to the prevailing hypoxemia is increasing with time. How are ventilatory acclimatization and deacclimatization mediated? These processes are complex and multifaceted and, to date, have been only partly resolved. We now examine hypotheses that include separate, independent contributions from peripheral and central chemoreceptors, as originally proposed 50 years ago, as well as current hypotheses that incorporate newer (and controversial) concepts of cardioventilatory control based on plasticity of chemosensitivity, multiple sites of hypoxic sensing, interdependence of central and peripheral chemoreceptors, and an upregulation of central nervous system (CNS) neurons comprising respiratory and sympathetic regulatory pathways.
normocapnic levels (via increased inspired fraction of CO2), reduced, and PCO2 in arterial blood and CSF rose over the first acid direction as the level of hyperventilation was gradually or “deacclimatization” from hypoxia, CSF pH changed in an equivalent to, or alkaline to, sea level control values in the face of continued hyperventilation (25). Equally important, over time during recovery in normoxia (over 24 h of normoxic restoration) in resting sea level (SL) natives sojourning at 4,300 m altitude (Mt. Evans, CO). Note the alkalization of arterial plasma and to a nearly identical extent cerebrospinal fluid (CSF), throughout the sojourn at high altitude. Changes in arterial PCO2 (PaCO2) reflect the degree of hyperventilation according to the alveolar gas equation: PaCO2 = 863/[Vd/Vt] × (1 – Vd/Vt), where PaCO2 is alveolar PCO2, Vd is minute ventilation, Vt is CO2 production, Vd is dead space volume, and Vt is tidal volume. In this example at 4,300 m, the 13- to 15-Torr total reduction in PaCO2 represents a 35–40% increase in alveolar ventilation from chronic normoxia to 10–11 days in hypoxia. PaO2, arterial PO2. [Adapted from Forster et al. (35).]

![Fig. 1. Time course of ventilatory acclimatization to hypoxia (over 11 days) and deacclimatization from hypoxia (over 24 h of normoxic restoration) in resting sea level (SL) natives sojourning at 4,300 m altitude (Mt. Evans, CO).](http://jap.physiology.org/)

Drive to breathe back to normal, which, when combined with a constant excitatory input from the hypoxic carotid chemoreceptors, would gradually increase ventilation, thereby accounting for time-dependent ventilatory acclimatization. Then, on acute restoration of normoxia and reduction of peripheral chemoreceptor inputs, the small initial increase in arterial PCO2 would acidify the CSF (with an already reduced [HCO3−]) and maintain hyperventilation at greater than control (chronic normoxic) levels until CSF [HCO3−] and pH were gradually restored to normal (17, 53, 70). This attractive, integrative hypothesis has been shown to be unlikely for several reasons.

1) CSF pH during acclimatization was shown to be incompletely compensated with the same time course and to the same extent (i.e., 60–70%) as that in arterial plasma. Thus CSF alkalinity increased or remained constant as hyperventilation intensified over time (23, 86) (see Fig. 1). Similarly, on acute reoxygenation following acclimatization, CSF pH was either equivalent to, or alkaline to, sea level control values in the face of continued hyperventilation (25).

2) Equally important, over time during recovery in normoxia or “deacclimatization” from hypoxia, CSF pH changed in an acid direction as the level of hyperventilation was gradually reduced, and PCO2 in arterial blood and CSF rose over the first 24 h of restoration of normoxia (25).

Thus, during either acclimatization to or recovery from chronic hypoxia, CSF pH appeared to be primarily determined by, rather than a determinant of, ventilatory acclimatization and deacclimatization. These data, obtained by measuring lumbar CSF acid-base status in humans, were confirmed via cisternal CSF measurements in nonhuman species (11, 25).

Finally, arterial hypocapnic alkalosis does not appear to be required for ventilatory acclimatization to or deacclimatization from hypoxia. When end-tidal PCO2 was precisely controlled at normocapnic levels (via increased inspired fraction of CO2) over several hours of constant hypoxia, a normal, time-dependent ventilatory acclimatization occurred in awake goats (9). Similarly, in humans, following many hours of hypoxic exposure, significant hyperventilation continued on acute restoration of normoxia (or acute hyperoxia) whether end-tidal PCO2 was maintained normocapnic or allowed to fall during the hypoxic exposure (32, 79). Furthermore, spontaneous hyperventilation was shown to persist following 26 h of voluntarily maintained hypocapnia in humans, and the level of this spontaneous, sustained hyperventilation was greater when the day-long hypocapnia was accompanied by hypoxia. This additional sustained stimulatory effect of hypoxemia on ventilation in the posthypoxic period occurred even though the arterial and CSF pH were identical (and significantly alkaline to normocapnic control levels) at the termination of both the normoxic and hypoxic hypocapnic periods (26).

**CAROTID CHEMORECEPTOR SENSITIZATION**

There is now substantial evidence showing the critical importance of carotid chemoreceptors and their time-dependent sensitization to ventilatory acclimatization to chronic hypoxia.

1) Bilateral carotid body (CB) denervation prevents ventilatory acclimatization to high altitude, even in the face of very severe levels of hypoxemia (PaO2, 29–31 Torr) (75). Even though brain lactic acidosis is greatly augmented and brain intracellular acidosis occurs in these conditions of extreme hypoxia (56), this is not sufficient, in the absence of carotid chemoreceptors, to elicit ventilatory acclimatization.

2) Recordings of single-unit carotid sinus nerve (CSN) activity in anesthetized goats showed an increase and then a plateau over the initial hour of hypoxia, but thereafter increased progressively over the remaining 3 h (58). These data demonstrated that CB sensitization occurs relatively early in the time course of exposure to hypoxia. Cross-sectional studies in anesthetized cats also confirmed that several days of hypoxic exposure elicited increases in CSN activity at any given PaO2 during superimposed acute hypoxia (3, 84). Upregulation of neuromodulators ATP (42), endothelin-1 (16), and angiotensin II (43) have all been implicated in this carotid chemoreceptor-specific sensitization (64).

3) When the carotid chemoreceptor of the awake goat was isolated and perfused with hypoxic blood for 6 h (via an extracorporeal gas exchanger), ventilatory acclimatization proceeded normally (see Fig. 2). Time-dependent ventilatory acclimatization did not occur (i.e., beyond the acute response) if the isolated, perfused carotid chemoreceptor was stimulated with hypercapnia, rather than hypoxia (8).

4) Increased protein expression occurred in rat carotid chemoreceptors over the first few days of moderate hypoxic exposure (85), and these newly generated type I glomus cells in the CB remained for several weeks after return to normoxia (85). Thus, in contrast to the hypoxic-induced apoptosis or cell death often reported in the CNS (2), the carotid chemoreceptor glomus cells appear to thrive and multiply under conditions of sustained oxygen lack.

While the critical role of CB sensitization in ventilatory acclimatization to hypoxia seems clear, it is less clear that this sensitization, by itself, accounts for the continued hyperventilation on acute return to normoxia. On the positive side, in the rat, Chen et al. (16) reported an elevation in CSN activity (above that in chronic normoxia) on restoration of acute normoxia after the third day (but not during the first 2 days) of hypoxic exposure. Furthermore, as noted above, new type I
glomus cells in the CB remained for several weeks after return to normoxia (85). On the negative side, the CSN activity was shown to return immediately to control on reoxygenation after 4 h of rising activity during isocapnic hypoxia in the anesthetized goat (10). Furthermore, even after hypoxic acclimatization was complete in the intact animal, bilateral CB denervation reduced, but did not eliminate, continued hyperventilation on acute restoration of normoxia (3).

ENHANCED CNS TRANSLATION OF CAROTID CHEMORECEPTOR INPUT

Dwinell and Powell used a unique approach in the anesthetized rat to show that 1 wk of hypoxia significantly increased the phrenic nerve response to supramaximal electrical stimulation of the CSN, as measured in a background of acute hyperoxia following prolonged hypoxic exposure (29) (see Fig. 3). These data suggest that sensitivity is increased at the level of those CNS neurons concerned with translation of CSN input into ventilation (also see below). Indirect findings in humans (36) and rats (87) also showed that chronic hypoxia markedly augmented the ventilatory response to a pharmacological CB stimulus (doxapram HCl), again when the stimulus was applied in an acutely hyperoxic background following acclimatization to moderate hypoxia (36).

In summary, the available data would attribute ventilatory acclimatization and deacclimatization to both time-dependent sensitization of carotid chemoreceptor sensory input, as well as a “central enhancement” of this input. We now discuss two potential means whereby this central enhancement might occur, namely via hypoxic-sensitive neurons in the CNS and/or as a consequence of central/peripheral chemoreceptor interdependence.

CNS Hypoxia

Acute CNS hypoxia in anesthetized animals resulted in no change in ventilation or a ventilatory depression (50, 57, 83). In awake, CB denervated animals, physiological levels of hypoxia usually have no significant effect on ventilation (13, 19). In contrast, when awake or sleeping animals with a vascularity isolated, intact carotid chemoreceptor that is perfused with normoxic, normocapnic blood are exposed to hypoxia via reduced inspired fraction of O2, a dose-dependent mildly tachypneic hyperventilation is observed. This response is initiated within 20–25 s of hypoxic onset, persists for 25 min or longer, and amounts to ~20–30% of the total ventilatory response to combined CB and CNS hypoxia (11, 19, 30) (see Fig. 4). These findings are consistent with the hypoxic-induced depolarization of many (but not all) cardiorespiratory neurons in the ventral-lateral medulla (59, 67). Given the tachypneic nature of the ventilatory response to CNS hypoxia in the awake animal (Fig. 4), this hyperventilatory response might also be attributed to depression of cortical neurons, which, in turn, would remove the inhibitory influence normally exerted by the cortex on “rate-facilitating” neurons in the diencephalon (80).

So, acute CNS hypoxia, per se, elicits ventilatory stimulation in the unanesthetized animal so long as an intact carotid chemoreceptor provides tonic (normal) input to the medulla. However, use of the isolated carotid chemoreceptor preparation in the goat exposed to 6 h of systemic hypoxemia (with isolated carotid bodies maintained normoxic and normocapnic) showed that sustained CNS hypoxia, per se, in the absence of increased carotid chemoreceptor stimulation, does not elicit a further time-dependent hyperventilation, i.e., beyond that obtained in acute CNS hypoxia (14). These negative findings speak against a time-dependent effect of CNS hypoxia per se. However, the possibility remains that the sustained increases in CSN activity in chronic hypoxia may enhance the stimulatory effect of CNS hypoxia and possibly other inputs to the autonomic control system as well (also see SUMMARY below).

Fig. 3. Increased response of phrenic nerve activity to carotid sinus nerve (CSN) electrical stimulation in anesthetized rats in chronic normoxia and in acute normoxia following seven days in hypoxia. [From Dwinell and Powell (29).]
Peripheral Chemoreceptor Influences On Central CO₂ Chemosensitivity

Recent evidence points to an interdependence of central medullary chemoreceptor activity on input from several sources. Guyenet and associates (38, 39) have recorded directly from CO₂ sensitive neurons in the retrotrapezoid nucleus (RTN) of the rat medulla. They found 1) that a direct glutaminergic pathway exists from the carotid chemoreceptors to the RTN; 2) that central CO₂ chemosensitive neurons also increased their activity in response to systemic hypoxia or to sodium cyanide, and that this response was eliminated following CB denervation; and 3) that inputs to the RTN from other areas, such as the hypothalamus and pulmonary stretch receptors from the lung, also influence the activity of RTN CO₂-sensitive cells. In other words, the responsiveness of the central CO₂ chemoreceptors in the RTN is not dependent only on the CO₂/H⁺ in their immediate environment (23, 70). Rather, in addition, they appear to also be dependent on the magnitude and source of several synaptic inputs that these neurons receive, and the carotid chemoreceptors are an important source of input affecting central chemoreceptor function.

The functional consequences of these neuronal connections to ventilatory control have been addressed in a variety of experimental preparations. The findings remain highly controversial, as summarized recently in a three-sided debate with proponents representing additive, hypoadditive, or hyperadditive effects on ventilation resulting from carotid chemoreceptor-central chemoreceptor interactions (28, 81, 88). We reasoned that, given the neuronal interconnections (39), the testing of their functional importance would require an experimental preparation wherein chemoreceptors were anatomically separated, major sources of influence on both sets of chemoreceptors were uncompromised, and in which chemosensitivity remained in the physiological range. Accordingly, we used the isolated, perfused CB preparation in the awake canine in which we superimposed central hypercapnia (via increased inspired fraction of CO₂) on a background of normal, inhibited or stimulated input from the isolated carotid chemoreceptor. As summarized in Fig. 5 (12), we found a hyperadditive effect of
carotid chemoreceptor input on central chemoreceptor CO2 responsiveness, whereby stimulating the isolated CB with hypoxia increased and inhibiting CB input via hyperoxic, hypocapnia markedly reduced the ventilatory response to central CO2. These findings are consistent with the substantial suppressive effect of bilateral CB denervation on ventilatory responses to focal medullary CO2-induced acidosis in the awake goat (44), to steady-state hyperoxic CO2 inhalation in the awake (68) or anesthetized dog (6) and awake human, as well as the so-called “late phase” CO2 ventilatory response in the human (5, 21, 31). We propose that this hyperadditive effect of carotid chemoreceptor output on central chemoreceptor gain (see Fig. 6) might contribute importantly to time-dependent ventilatory acclimatization as carotid chemoreceptor sensitivity increases over time in hypoxia. Moreover, we suspect that the time-dependent increase in carotid chemoreceptor input also elicits changes in elements of the control system itself that might contribute to the continued, gradually diminishing hyperventilation upon return to normoxia (also see SUMMARY below). Of course this possibility awaits resolution of the controversy over the functional nature of peripheral-central interdependence.

SYMPATHETIC ACCLIMATIZATION/DEACCLIMATIZATION TO HYPOXIA

There are many similarities in the ventilatory and sympathetic vasconstrictor responses to chronic hypoxia (18, 47). Like ventilation, muscle sympathetic nerve activity (MSNA) in humans increases slightly on acute hypoxic exposure, is substantially further augmented over several days at high altitude, and then remains elevated on return to normoxia, even after up to 3–5 days in normoxia (40) (see Fig. 7). As explained above for ventilation, the carotid chemoreceptors are also critical to the acute sympathetic response, and carotid chemoreceptor sensitization and its central amplification coincides with the time-dependent increase in MSNA. Furthermore, the continued elevation in MSNA on return to normoxia may rely, at least in part, on residual, sustained increases in CSN activity (62) (see also SUMMARY below). Other similarities are that only hypoxic and not CO2-induced increases in MSNA elicited a persistent after-effect on normoxic restoration (90), and also that hypoxic receptors in the rostral ventrolateral medulla have been shown to drive a sympathetic response to CNS hypoxia (77). On the other hand, a clear difference between sympathetic vs. ventilatory responses to hypoxia in the human is that a substantial, sustained after-effect of hypoxia on elevating MSNA (upon return to normoxia) remains elevated on return to normoxia, even after up to 3–5 days in normoxia (40).
return to normoxia) occurred after only 20–30 min of hypoxic exposure and at a time when ventilation had returned completely to control levels (55, 90).

SUMMARY

Different sets of overlapping mechanisms may account for ventilatory and sympathetic acclimatization to, vs. deacclimatization from, chronic hypoxia. First, it is likely that CB sensitization, per se, contributes importantly to the time-dependent ventilatory acclimatization during the hypoxic exposure. Furthermore, we speculate that this CB sensitization in chronic hypoxia also contributes to the “central enhancement” of CSN input by further sensitizing hypoxic-sensitive respiratory neurons in the CNS and/or CO2-sensitive neurons in the RTN. On the other hand, given the continued hyperventilation obtained on the acute application of normoxia or even hyperoxia, we must also conclude that an ongoing raised CSN activity (in the posthypoxic period) is not required to be present for this continued hyperventilation to occur. Rather, as has been demonstrated recently in rodent models of prolonged intermittent hypoxia with attendant CB sensitization (62), the persistent elevation of respiratory motor output and sympathetic nerve activity on return to normoxia was dependent on ongoing tonic hyperactivity of neurons at the level of the paraventricular nucleus (72) and the rostral ventrolateral medulla (37, 49, 74). These sustained neuroadaptive responses coincided with up-regulation of the renin-angiotensin system (33) and of angiotensin II type 1 (AT1) receptors in the paraventricular nucleus (20). Based on these findings, we predict that chronic constant hypoxia may also elicit chemoreceptor input-dependent long-term CNS adaptive responses that induce tonic hyperactivity and acute hyperexcitability of neurons comprising respiratory and sympathetic regulatory pathways with cardiorespiratory effects that outlast the hypoxic stimulus.

PHYSIOLOGICAL CONSEQUENCES OF CHEMORECEPTOR SENSITIZATION AND CARDIORESPIRATORY ACCLIMATIZATION

Excessive Hyperventilation

The time-dependent increases in ventilation in hypoxia are critical to minimizing the reduction in alveolar PO2 (and therefore arterial O2 saturation) as inspired PO2 is reduced with increasing altitude. For example, note the progressive rise in PaCO2 over time in Fig. 1, amounting to an increase in arterial HbO2 saturation from 75% on day 1 to 85% on day 14. The enhanced hyperventilation and accompanying high alveolar PO2 are especially critical during heavy-intensity exercise in the sojourner at high altitude to minimize the magnitude of exercise-induced arterial hypoxemia in the face of an exercise-induced widening of the alveolar PO2 to PaO2 difference (24) (see also Fig. 8). At the same time, during exercise in chronic hypoxia, the “excess” hyperventilation means a markedly increased work of breathing (82), as well as increased susceptibility to expiratory flow limitation, leading to hyperinflation and severe dyspneic sensations. Accordingly, studies using mechanical ventilation to unload the respiratory muscles have shown that this excessive ventilation and work of breathing in hypoxia may contribute significantly to exercise performance limitation because of enhanced respiratory muscle fatigue, return to normoxia) occurred after only 20–30 min of hypoxic exposure and at a time when ventilation had returned completely to control levels (55, 90).

SUMMARY

Fig. 8. Contrast of the ventilatory and respiratory gas exchange responses to exercise at 3,100-m altitude in acclimatized sojourners (solid line) vs. native or long-term resident highlanders (dashed line). VO2, O2 consumption; Qc, pulmonary blood flow. Note the greater hyperventilation (lower PaCO2) during all exercise levels in the sojourners in contrast to the near isocapnic hyperpnea in the highlander. However, the PaO2 is similar between the groups because the lung diffusion capacity (DLCO) is greater, and the alveolar PO2-to-PaO2 difference ([A-a]DO2) narrower in the highlander. Shading indicates confidence limits around the mean. [Data compiled from Refs. 15, 24.]

Fig. 9. Acute effects of cyclical sleep apneas and attendant intermittent hypoxemia on MSNA and systemic blood pressure in a patient with obstructive apnea during sleep at SL. Each apneic event terminated with a transient arousal pattern in the EEG (not shown). [Adapted from Dempsey et al. (27).]
resulting in a faster rate of development of locomotor muscle fatigue (1). In turn, this link between respiratory muscle work and fatigue and locomotor muscle fatigue may be explained by a sympathetically mediated redistribution of blood flow from locomotor to respiratory muscles (41).

In contrast to the sojourner, most long-term high-altitude residents or natives have blunted (rather than enhanced) hypoxic chemosensitivity at both rest (34, 54) and during exercise (24). Thus highlanders show only minimal hyperventilation during exercise (i.e., beyond that at rest), in their hypoxic environment. However, they preserve their PaO2 and O2 saturation during exercise at about the same level as in the markedly hyperventilating sojourner (24). This highly efficient preservation of arterial oxygenation occurs because, unlike the sojourner, the long-term resident highlander has undergone adaptive morphological changes in the lung parenchyma, which produce a greatly enhanced alveolar-capillary diffusion surface area and, therefore, minimizes the alveolar PO2 to PaO2 difference during exercise (15, 24, 45) (see Fig. 8).

**Excessive Sympathetic Vasoconstrictor Activity**

Theoretically, the enhanced, time-dependent increase in sympathetic vasoconstrictor activity in chronic hypoxia (40, 66) should help maintain systemic blood pressure by opposing the vasodilatory effects of systemic local hypoxemia. In acute hypoxia, this balance appears to occur as systemic blood pressure is normally unchanged from control. However, after days to weeks at high altitudes, the vasoconstrictor effects of excessively high sympathetic outflow in the sojourner appear to dominate, as manifested in the occurrence of systemic hypertension throughout the waking and sleeping hours (66, 89). These dominant vasoconstrictor hypertensive effects also persist for several days on return to sea level (71, 89).

Of clinical relevance, a persistent sympathoexcitatory effect in the normoxic recovery period following acute hypoxia has also been observed at sea level (90). This “carry-over” effect on MSNA has been implicated in the high prevalence of persistent daytime systemic hypertension in patients with severe obstructive sleep apnea accompanied by nocturnal intermittent hypoxemia (see Fig. 9) (4, 91). Furthermore, when the intermittent hypoxemia normally attending obstructive sleep apnea was mimicked (via inspired fraction of O2 manipulation) in healthy young adults for 8–10 h/day over 2- to 3-wk periods, significant increases occurred in daytime (normoxic) MSNA and systemic BP, together with an increased hypoxic ventilatory response, reductions in baroreceptor sensitivity, and increased inflammatory markers (63, 78). Studies in the rodent have shown that chronic intermittent hypoxemia sensitizes carotid chemoreceptors so that CNS activity remains elevated on acute return to normoxia (65). A contributive role of inflammatory cytokines (46) and an upregulation of angiotensin II AT1 receptors (52) in this CB sensitization has been proposed. The persistence of elevated sympathetic nerve activity following intermittent hypoxemia also coincides with neuroadaptation at several sites of cardiorespiratory regulation within the CNS (see SUMMARY section above). In the healthy sojourner to high altitude, periodic breathing during sleep is common and attributable to increased carotid chemoreceptor gain effects on sensitizing the hypocapnia-induced apneic threshold (22). It is likely that this nocturnal periodic breathing with attendant intermittent hypoxemia contributes to the sojourner’s daytime hypertension and heightened MSNA.

It is important to determine if these same substantial after-effects of intermittent hypoxemia on the cardiovascular system are also produced by the popular practice of “live high:train low” training regimens (51). Although these athletes are exposed to constant environmental hypoxia (i.e., reduced inspired PO2) for up to 10–12 hours/day, cyclical intermittent arterial hypoxemia will occur when periodic breathing is present. Thus negative cardiovascular consequences are most likely to occur in those who choose exposure altitudes greater than 3,000 m at which periodic breathing during sleep and attendant intermittent hypoxemia are prevalent (7). Perhaps the deleterious effects of repetitive, cyclical type of intermittent hypoxemia on endothelial function and the hypersensitization of the carotid chemoreceptors leading to increased sympathetic vasoconstriction, especially during exercise (76), may counteract the normal benefits of physical training on blood flow distribution and O2 transport. In turn, these negative consequences may account for at least some of the marked heterogeneity of changes in exercise performance routinely experienced with live high-train low regimens (51, 73). These hypotheses concerning the potential complex cardiovascular consequences of sleeping in hypoxia remain to be tested. In the meantime, we strongly urge those conducting sleep high-train low regimens to routinely measure O2 saturation as a marker of periodic breathing and intermittent hypoxemia during sleep in the hypoxic environment and to monitor systemic blood pressure in the posthypoxic periods. Hopefully, this monitoring process would lead to a practice of titrating the inspired PO2 in the individual athlete to achieve a level of nocturnal hypoxemia (i.e., duration and severity) sufficient to stimulate a positive erythropoietic effect without triggering cyclical periodic breathing and intermittent hypoxemia. We would predict that achieving this optimal combination will present a substantial challenge.

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**AUTHOR CONTRIBUTIONS**


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