Peripheral chemoreceptors in health and disease

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Prabhakar, Nanduri R., and Ying-Jie Peng. Peripheral chemoreceptors in health and disease. J Appl Physiol: 96: 359–366, 2004; 10.1152/japplphysiol.00809.2003.—Peripheral chemoreceptors (carotid and aortic bodies) detect changes in arterial blood oxygen and initiate reflexes that are important for maintaining homeostasis during hypoxemia. This mini-review summarizes the importance of peripheral chemoreceptor reflexes in various physiological and pathophysiological conditions. Carotid bodies are important for eliciting hypoxic ventilatory stimulation in humans and in experimental animals. In the absence of carotid bodies, compensatory upregulation of aortic bodies as well as other chemoreceptors contributes to the hypoxic ventilatory response. Peripheral chemoreceptors are critical for ventilatory acclimatization at high altitude. They also contribute in part to the exercise-induced hyperventilation, especially with submaximal and heavy exercise. During pregnancy, hypoxic ventilatory sensitivity increases, perhaps due to the actions of estrogen and progesterone on chemoreceptors. Augmented peripheral chemoreceptors have been implicated in early stages of recurrent apneas, congestive heart failure, and certain forms of hypertension. It is likely that chemoreceptors tend to maintain oxygen homeostasis and act as a defense mechanism to prevent the progression of the morbidity associated with these diseases. Experimental models of recurrent apneas, congestive heart failure, and hypertension offer excellent opportunities to unravel the cellular mechanisms associated with altered chemoreceptor function.

carotid bodies; aortic bodies; exercise; high altitude; apneas; hypertension; congestive heart failure; sympathetic nerve activity; ventilation

AN ADEQUATE SUPPLY OF OXYGEN (O2) is essential for mammalian cells. Peripheral chemoreceptors monitor changes in arterial blood O2, and within seconds after the onset of hypoxia they trigger cardiorespiratory changes (i.e., increase in breathing and blood pressure), which are important for maintaining O2 homeostasis. Conventionally, peripheral chemoreceptors are thought to comprise carotid and aortic bodies. However, tissues similar to carotid and aortic bodies have also been described in thorax and abdomen, which are often called “paraganglion” and may serve as additional chemoreceptors (11, 16). The purpose of this mini-review is to highlight the importance of peripheral chemoreceptors for maintaining O2 homeostasis during hypoxia associated with physiological as well as pathophysiological situations.

Mechanisms of O2 Sensing at Peripheral Chemoreceptors

Of all the anatomically identified chemoreceptor tissues, carotid bodies are the most thoroughly studied with respect to the mechanism of O2 sensing. This section provides a brief summary of the O2-sensing mechanisms at the chemoreceptors. Detailed account of sensory transduction at the chemoreceptors can be found in several excellent reviews on this topic (25, 45, 67). Carotid bodies are composed of glomus cells (also called type I), which are of neuronal phenotype and contain a variety of neurotransmitters, whereas the sustancitcular cells (also called type II cells) resemble glial cells. Glomus cells are in functional contact with the afferent nerve endings. Several lines of evidence suggest that glomus cells are the initial site(s) of sensory transduction. Presently, it is believed that hypoxia releases transmitter(s) from glomus cells, which in turn by depolarizing the sensory nerve ending leads to an increase in sensory discharge. Two main theories have been proposed to explain the mechanism(s) by which hypoxia triggers transmitter release from glomus cells. One hypothesis assumes that a K+ -channel protein is an O2 sensor and that hypoxia depolarizes glomus cells by inhibiting the K+ channel, leading to an increase in cytosolic Ca2+, resulting in transmitter(s) release. The other theory proposes that a heme protein or a related protein (either cytosolic or of mitochondrial origin) is an O2 sensor and that a biochemical event associated with the redox state of the protein triggers transmitter release. Both hypotheses are not mutually exclusive; perhaps the purported sensors work in concert such as a “chemosome” (i.e., aggregate of sensors), operating over a wide range of P02 values.

There is considerable evidence for the involvement neurotransmitters in the transmission of the hypoxic signal from glomus cell to the nerve ending. Carotid body expresses as many types of neurotransmitters as the brain tissue, and they are coreleased during hypoxia (39, 42, 65). Some of them are excitatory and some inhibitory to the sensory activity. There are two fundamental questions with respect to the sensory
transmitters. First, which of the transmitter(s) is responsible for sensory excitation? And second, what is the significance of inhibitory transmitters in sensory transmission? The proposed transmitters that mediate the sensory excitation by hypoxia include acetylcholine, substance P, and adenosine triphosphate (42). It was proposed that inhibitory transmitters prevent over-excitation of the sensory activity caused by excitatory transmitters acting as a push-pull mechanism and thus contribute to the maintenance of sensory excitation during long periods of hypoxia (67).

Although hypoxia augments sensory discharge of both carotid and aortic bodies, it was proposed that aortic chemoreceptors sense O2 saturation, whereas carotid bodies monitor P02 (44). This notion was based on the finding that carboxyhemoglobinemia causes marked stimulation of aortic bodies, whereas it has no effect on the carotid body sensory activity. Therefore, whether the O2-sensing mechanism(s) described at the carotid body also operates at the aortic body remains uncertain.

**CHEMORECEPTOR FUNCTION UNDER PHYSIOLOGICAL CONDITIONS**

**Relative Contribution of Carotid and Aortic Bodies to the Hypoxic Ventilatory Response**

*Experimental animals.* Although acute hypoxia augments the sensory discharge of both carotid and aortic bodies (43), there is considerable evidence suggesting reflexes from the carotid body are more important in preserving O2 homeostasis, whereas aortic chemoreceptors become important only in the chronic absence of carotid bodies. In experimental animals, chronic removal of carotid bodies or bilateral sectioning of carotid sinus nerves caused attenuation of the hypoxic ventilatory response that lasted several days to weeks. Subsequently, there was a recovery of the hypoxic ventilatory response, which implied compensatory upregulation of noncarotid body chemoreceptor mechanisms. In cats, Smith and Mills (76) reported 85% recovery of the hypoxic ventilatory response after 215–260 days of bilateral sectioning of sinus nerves. Bisgard et al. (6) observed 30% recovery of the hypoxic ventilatory sensitivity in ponies 22 mo after sinus nerves were sectioned. The restoration of hypoxic ventilatory sensitivity disappeared after the aortic nerve was sectioned, suggesting that aortic body reflexes maintain hypoxic ventilatory drive. Earlier studies on rats have shown that electrical stimulation of the aortic nerve produces little or no change in breathing (73). These findings led to the belief that aortic bodies contribute little to the hypoxic ventilatory response in rats. However, after chronic sectioning, carotid sinus nerve hypoxic ventilatory sensitivity was partially restored in rats (7, 51), a finding consistent with observations in other species. Kline et al. (40) reported that carotid body sensory response to hypoxia was markedly depressed in mice partially deficient in hypoxia-inducible factor 1α transcription factor subunit. Yet, these mice exhibit normal hypoxic ventilatory response, which is mediated by noncarotid body afferents innervated by the vagus nerve. These observations provide evidence for the importance of noncarotid body afferents in mice for maintaining ventilatory hypoxic sensitivity in the absence of functional carotid bodies. Thus in almost all experimental animal species examined thus far, hypoxic ventilatory sensitivity is restored in the chronic absence of carotid bodies, and this effect is mediated by compensatory upregulation of noncarotid body afferents.

*Humans.* In the 1940s, it was thought that carotid bodies were responsible for asthma and that resection of carotid bodies might offer a therapeutic intervention. Honda and Tani (35) performed a number of physiological studies on human subjects 20 yr after surgical removal of carotid bodies. They studied 11 patients with bilateral carotid body resection, 11 patients with unilateral removal, and 5 control subjects matched in age and pulmonary function. In carotid body resected subjects, arterial PCO2 and pH were normal, whereas arterial PO2 was slightly reduced. Baroreceptor function is preserved in these subjects, as evidenced by bradycardia in response to Valsalva’s maneuver, and none of these subjects was hypertensive. Ventilatory response to progressive hypoxia was markedly attenuated or abolished in bilateral carotid body-resected subjects, whereas it was significantly reduced in unilateral carotid body subjects compared with normal subjects with intact carotid bodies (35). On the other hand, ventilatory response to transient hypoxia (single-breath hypoxia) was reduced but not completely abolished in bilateral carotid body-resected subjects (35). On the basis of these observations, it was suggested that carotid bodies are primarily responsible for ventilatory stimulation during progressive hypoxia, whereas during transient hypoxia, aortic bodies contribute to 5–10% of the ventilatory responses (34). Other investigators (32, 50, 82) also reported blunted ventilatory response to progressive hypoxia in carotid body-resected subjects. Lack of restoration of the hypoxic ventilatory response in carotid body-resected subjects seems to suggest that humans do not exhibit upregulation of noncarotid body afferents in the chronic absence of carotid bodies. It should, however, be noted that these subjects had a history of asthma, and the severity of the disease in these subjects is uncertain. It is known from the work of Hudgel and Weil (36) that hypoxic and hypercapnic ventilatory responses are depressed in humans who have severe asthma. Therefore, whether the attenuation of the hypoxic ventilatory response in carotid body-resected subjects is due to the consequence of asthma or due to the absence of compensatory upregulation of noncarotid body chemoreceptors remains uncertain. Thus there are some important limitations with human studies.

It is evident from the studies on experimental animals that carotid bodies are important for mediating ventilatory response to hypoxia under normal conditions. In the chronic absence of carotid body, upregulation of other peripheral chemoreceptors, especially the aortic chemoreceptors, restores the hypoxic ventilatory response, suggesting that the ventilatory control system exhibits a considerable degree of plasticity to maintain O2 homeostasis. However, little is known about the mechanism(s) associated with upregulation of noncarotid body chemoreceptors. It is likely that O2-sensing mechanisms are upregulated at the noncarotid body receptors (i.e., at the level of sensory receptor). Alternatively, there may be enhanced processing of afferent information at the central neurons, which receive peripheral chemoreceptor inputs. Forster (18) suggested that chronic absence of carotid body inputs upregulates efferent motor pathways of the hypoxic ventilatory chemoreflex that are under serotonergic control.
Role of Peripheral Chemoreceptors in Neontal Ventilatory Control

In fetal and neonatal animals, sensory activity of the carotid body responds poorly to hypoxia. However, carotid body responds normally to hypoxia a few days to weeks after birth (see Ref. 14), suggesting maturation of the sensory response. It was proposed that maturation of the hypoxic ventilatory response critically depends on the developmental maturity of peripheral chemoreceptors. Donnelly and Haddad (15) studied the effects of sectioning of sinus nerves early in life in piglets 3–9 days of age. Bilateral sectioning of sinus nerves resulted in hypoventilation, and this effect was pronounced after combined sectioning of sinus and aortic nerves. Sinus denervation alone as well as in combination with aortic nerves led to increased incidence of apneas and mortality. Cote et al. (10) also observed irregular breathing after bilateral sectioning of carotid bodies in neonatal animals but did not observe increased mortality. In contrast, Lowry et al. (49) were unable to observe either irregular breathing or significant hypoventilation or mortality after bilateral sectioning of sinus nerves in 2- to 5-day-old piglets by using a lateral surgical approach. Lowry et al. (49) attributed the irregular breathing observed by Donnelly and Haddad (15) to the damage of upper airway innervation during denervation of carotid bodies while using a midline surgical approach. Absence of hypoventilation observed by Lowry et al. (49) is consistent with the idea that carotid body afferents are immature immediately after birth. Furthermore, these authors hypothesized that, in piglets (<5 days of age), when carotid bodies are removed aortic chemoreceptors provide enough stimulation to breathing and thus prevent hypventilation. This hypothesis would suggest that, in the neonatal period, unlike carotid bodies, aortic chemoreceptors are functionally mature. This interesting idea, however, needs to be substantiated by recording sensory activity of the aortic body in neonatal animals. In another study, Lowry et al. (48) examined the effects of bilateral carotid body denervation on ventilation in neonatal goats. In these experiments, sinus nerves were sectioned at 1–3 days of age, and carotid body denervation was verified by the absence of ventilatory stimulation by systemic administration of sodium cyanide. By 3 mo of age, there were no differences in basal ventilation or in the ventilatory responses to hypoxia or CO2 between sinus nerve-sectioned and control animals. Intracarotid administration of cyanide did not produce ventilatory stimulation, suggesting that carotid bodies were not reinnervated. Therefore, these investigators attributed the recovery of the hypoxic ventilatory response to other functional chemoreceptors that compensate for carotid bodies similar to that described in adult animals. It was proposed that the relative contribution of noncarotid body afferents to the plasticity of ventilatory control during hypoxia is greater in neonates than in adult animals (49).

Peripheral Chemoreceptors and Exercise

Reflexes from peripheral chemoreceptors have been implicated in ventilatory stimulation during exercise (59, 88, 90, 94). Ventilatory changes during exercise can be categorized into three phases: phase I, rapid increase in ventilation that occurs at the start of the exercise; phase II, exponential increase in ventilation during exercise; and phase III, steady-state, nonlinear increase in ventilation (above anaerobic threshold). Based on the studies with exercising human subjects (88, 94), it was proposed that peripheral chemoreceptor reflexes contribute to ventilatory stimulation during phases II and III but not in phase I. Chemoreflexes maintain arterial PCO2 and prevent hypoxemia during phase II. They contribute up to 20% of the ventilatory drive during phase III, and the contribution may raise as much as 50% while exercising in hypoxic environment (arterial PO2 of ~50 Torr) (88, 94). Exercise hypopnea was depressed in carotid body-resected subjects compared with carotid body-intact subjects (33, 91). Stulbarg et al. (79) also noted decreased ventilatory response to exercise in three subjects with carotid body resection. These subjects became severely hypoxemic during exercise. It should, however, be noted that some of the carotid body-resected subjects had a history of asthma, which by itself depresses the hypoxic ventilatory response (36).

Although the studies on human subjects suggest a role for peripheral chemoreceptors in exercise-induced hyperventilation, observations from experimental animals are not entirely consistent with such a possibility. On the basis of the data from carotid body-denervated ponies and experiments on awake dogs and goats, Dempsey and Smith (12) concluded that carotid body chemoreceptors exert inhibitory influence to the respiratory motor output during heavy exercise. Forster and Pan (22) studied the role of carotid bodies in the control of breathing during submaximal exercise in humans and ponies. These investigators concluded that carotid bodies “fine tune” alveolar ventilation during submaximal exercise but do not provide primary drive for exercise hyperpnea. Although studies on human subjects suggest that peripheral chemoreceptors (carotid bodies) contribute to stimulation of breathing during exercise, it should be noted that much of the evidence is based on a variety of techniques that provide only an indirect assessment of peripheral chemoreceptor function. Direct monitoring of carotid body activity in humans is impossible, and it will be a technical feat in awake, exercising animals. Thus some of the controversies surrounding the role of peripheral chemoreceptors in exercise-induced hyperventilation are likely due to inherent technical limitations for assessing chemoreceptor function.

How do the peripheral chemoreceptors get stimulated during exercise? Exercise increases circulating catecholamine levels, which may stimulate chemoreceptors. Metabolic acidosis (lactic acid) has been thought to be a stimulus for peripheral chemoreceptors, especially during heavy exercise (90). Patients with McArdle’s syndrome (myophosphorylase deficiency) cannot catabolize glycogen and thus cannot generate lactic acid. However, these patients still respond with an increase in ventilation during heavy exercise as in normal subjects (60). It was proposed that a stimulus in addition to the lactic acid might be important for augmenting peripheral chemoreceptor activity. Paterson (59) reviewed the evidence for K+ as a potential stimulus to peripheral chemoreceptors during exercise. K+ is released from contracting muscle (53) and results in hyperkalemia. Systemic administration of K+ augments breathing, and sinoaortic denervation prevents this response (2, 3). K+ stimulates the carotid body activity, and this effect was potentiated by hypoxia and depressed by hyperoxia (2, 8). On the other hand, hypercapnia had no effect on K+-induced augmentation of the carotid body activity (8). It was proposed that K+ stimulates the carotid body activity by
Peripheral Chemoreceptors as Neuroendocrine Responses During Exercise

In addition to their role in ventilatory control, reflexes from carotid bodies also contribute to regulation of neuroendocrine responses in exercise in awake dogs (41). Exercise-induced glucagon and circulating norepinephrine levels were markedly attenuated in exercising dogs whose carotid sinus nerves were bilaterally sectioned 16 days before the experiment. Recently, it has been reported that low glucose inhibits K⁺ currents and increases catecholamine secretion from glomus cells of the carotid body (58), suggesting that carotid bodies, in addition to hypoxia, also sense changes in blood glucose levels. Stimulation of carotid body by low glucose might be an important mechanism for triggering neuroendocrine responses. However, further studies are needed to demonstrate that K⁺-channel inhibition by low glucose is translated to an increase in the sensory discharge of the carotid body.

Peripheral Chemoreceptors and Altitude Acclimatization

Acute ascent to high altitude results in a prompt increase in ventilation. When a sojourn at high altitude continues for hours to days, ventilation progressively increases, despite hypocapnia and respiratory alkalosis resulting from hyperventilation. The progressive increase in ventilation at high altitude is referred to as "ventilatory acclimatization" (92). An increase in hypoxic ventilatory response during a high-altitude sojourn was consistently seen in normal human subjects. Forster et al. (21) found that the hypoxic ventilatory response was nearly doubled at an altitude of 3,100 m in men. Sato et al. (74) examined in detail the hypoxic ventilatory response in normal human subjects exposed to increasing levels of high altitude. These investigators also found an augmented hypoxic ventilatory response at high altitude. Also, experimental animals exposed to simulated high altitude exhibit an augmented ventilatory response to hypoxia. Vizek et al. (87) found an increased hypoxic ventilatory response in cats exposed to 48 h of hypobaric hypoxia (barometric pressure of 440 mmHg). Similarly, goats exposed to chronic hypoxia exhibit an augmented ventilatory response to hypoxia (56). These examples illustrate that high-altitude exposure enhances the ventilatory response to hypoxia in both human subjects and experimental animals. Ventilatory acclimatization is of considerable physiological significance because it represents a primary defense against hypoxia. Failure to hyperventilate sufficiently on ascent to altitude likely contributes to acute mountain sickness, pulmonary edema, and cerebral edema. The magnitude of ventilatory acclimatization to high altitude, however, may vary with gender and be greater in females than in males (37).

The mechanism(s) associated with ventilatory acclimatization has been extensively investigated (see Ref. 20 for references). There is a large body of evidence suggesting that carotid bodies are critical for high-altitude ventilatory acclimatization (see Ref. 5 for references). In experimental animals, bilateral denervation of carotid bodies attenuates or abolishes ventilatory acclimatization (5, 19). Direct monitoring of carotid body sensory activity showed a progressive increase in afferent discharge with prolonged exposure to hypoxia in goats (56). Vizek et al. (87) found enhanced carotid body sensitivity in cats exposed to 48 h of hypobaric hypoxia. Barnard et al. (4) also reported increased carotid body activity in cats exposed to hypoxia for 28 days. Furthermore, human subjects who have undergone carotid surgery adapt rather poorly to high altitude (72), further supporting the idea that chemoreflexes are necessary for altitude acclimatization. Tatsumi et al. (84) reported decreased responsiveness of the carotid bodies and hypoxic ventilatory response in cats after 3–4 wk of exposure to 5,500-m altitude, suggesting that prolonged altitude exposure leads to diminished ventilatory hypoxic sensitivity, which is in part due to "desensitization" of the carotid body O₂-sensing mechanisms (92).

Several studies examined the mechanisms associated with carotid body adaptations to chronic hypoxia. Increased carotid body sensitivity during chronic hypoxia has been attributed to (1) changes in ionic conductances in glomus cells, (2) activation of second messengers, (3) decreased dopaminergic efferent inhibition of the carotid body (46), and (4) increased endothelin levels (see Ref. 42 for references). In most species, including humans, chronic hypoxia leads to enlargement of carotid bodies and hyperplasia of glomus cells (30). Electron microscopic analysis of carotid body from rats exposed to sustained hypoxia (10% O₂ for 3–4 wk) showed hyperplasia of type I cells, neovascularization, increased glomus cell volume, and decreased mean distance between endothelium and glomus cells (13). Whether morphological changes in the carotid body contribute to augmentation or "desensitization" of the carotid body during chronic hypoxia remains uncertain.

To establish summits at high altitudes, mountain climbers ascend from low to higher altitudes and then return to base camps for rest. These repeated brief ascents to altitudes are important for acclimatization and successful summit attempts (64). During brief ascents to altitudes, subjects experience episodic hypoxia. Several studies have reported that episodic hypoxia associated with repeated ascents to high altitude result in enhanced hypoxic but not hypercapnic ventilatory response (see Ref. 68 for references). Whether the increased hypoxic ventilatory sensitivity is due to heightened carotid body sensitivity to low O₂ and/or to enhanced processing of chemoreceptor inputs at the central nervous system remains uncertain.

Pregnancy

It has long been known that normal pregnancy is associated with increased resting ventilation and augmented ventilatory response to hypoxia and hypercapnia (93). The increased chemosensitive drive to ventilation is evident after week 20 of gestation, is correlated with elevated levels of progesterone and estradiol, and precedes an increase in metabolic rate (54). Enhanced hypoxic ventilatory chemosensitivity can be elicited in nonpregnant women by combined administration of progesterone and estrogen (71). Hannhart et al. (28) reported marked enhancement of carotid body sensory response to hypoxia in pregnant compared with nonpregnant control cats. These observations suggest that increased carotid body sensitivity to hypoxia contributes in part to elevated basal ventilation and augmented hypoxic ventilatory sensitivity in pregnant animals. Estrogen affects neuronal excitability by two mechanisms. One
is slow in onset and prolonged and is called the “genomic” effect; the other is rapid and of short duration and is called the “nongenomic” effect (52). Nuclear estrogen receptors (ER-α and ER-β) mediate the slow actions of estrogen, whereas the rapid actions (nongenomic actions) are associated with activation of G proteins, cAMP, mitogen-activated protein kinases, Ca^{2+} channels, and Ca^{2+} entry (see Ref. 52 for references). Determining which of these mechanisms contributes to estrogen-induced enhanced hypoxic sensitivity of the carotid body requires further investigation.

**CHEMORECEPTOR FUNCTION IN PATHOPHYSIOLOGICAL CONDITIONS**

Peripheral chemoreceptors have been implicated in various diseases, including sleep-disordered breathing, congestive heart failure (CHF), and certain forms of hypertension.

**Sleep-Disordered Breathing**

Much of the information on sleep-disordered breathing and its consequences on ventilatory control come from studies on patients with obstructive sleep apnea (OSA) and central apneas. Patients newly diagnosed for OSA exhibit augmented hypoxic ventilatory response. Narkiewicz et al. (55) reported striking augmentation of the hypoxic ventilatory response in OSA subjects who were relatively young (42 ± 2 yr of age), newly diagnosed for OSA, normotensive, and without history of prior medication. Their resting blood gases were comparable to those of control subjects. Similar augmentation of hypoxic ventilatory response was also reported by Cistulli and Sullivan (9) in patients with severe sleep apneas who had normal blood gases under awake, resting conditions. Augmented hypoxic ventilatory response was attributed to enhanced peripheral chemoreceptor sensitivity (38). Consistent with such a possibility is the finding that ventilatory depression with brief hyperoxic challenge (Dejour’s test, a measure of peripheral chemoreceptor sensitivity) was more pronounced in OSA patients than in control subjects (38, 83). Furthermore, glomectomized subjects with sleep apneas do not develop hypertension (see Discussion in Ref. 78). Because apneas are associated with intermittent hypoxia, Fletcher et al. (17) developed a rat model of intermittent hypoxia that mimicked the pattern of hypoxic episodes encountered during apneas (~20 s of 5% inspired O_{2}; 9 episodes/h; 8 h/day). Animals exposed to 30 days of intermittent hypoxia developed hypertension and increased sympathetic nerve activity, similar to that seen in patients with sleep apneas. Chronic bilateral sectioning of sinus nerves prevented the development of hypertension and increased sympathetic nerve activities (47). A recent report by Peng et al. (61) provides direct evidence for enhanced peripheral chemoreceptor sensitivity by intermittent hypoxia. These investigators recorded sensory activity of the carotid body in rats exposed to 10 days of intermittent hypoxia (15 s of 5% inspired O_{2}; 9 episodes/h; 8 h/day). They reported augmented carotid body sensory response to hypoxia. Furthermore, acute episodic hypoxia produced long-lasting activation carotid body sensory discharge that persisted for 1 h after termination of the stimulus in intermittent hypoxia-conditioned rats. A similar enhancement in hypoxic sensory response was also seen in ex vivo carotid body preparation, suggesting that the observed increase in the sensory discharge was not secondary to cardiovascular changes. Morphometric analysis revealed no significant changes in the carotid body from intermittent hypoxia-exposed animals. The effects of intermittent hypoxia were completely reversed after reexposure to 10 days of normoxia. These investigators attributed the enhanced carotid body sensitivity to oxidative stress caused by intermittent hypoxia.

Although the studies described above suggest augmented chemoreceptor sensitivity in the early stages of sleep apneas, there are several studies (24, 57, 69, 70) reporting depressed hypoxic ventilatory sensitivity in sleep apnea patients. However, the subjects that exhibited depressed hypoxic ventilatory sensitivity had a long history of sleep apneas for nearly 20 yr with an AHA index (apnea-hypopneas/h) of 60/h. The majority of them were hypercapnic under resting conditions (arterial P_{CO_{2}} of 52 ± 7 Torr; Ref. 24). Thus it is likely that hypoxic ventilatory sensitivity may get depressed with continued apneas for several years.

What are the functional consequences of altered chemoreceptor sensitivity to hypoxia during sleep apneas? It is possible that, in the early stages of apneas, increased chemoreceptor activation contributes to augmented hypoxic ventilatory response, increased sympathetic nerve activity, and blood pressure. These cardiorespiratory changes are beneficial in that they help to maintain adequate ventilation, arterial blood gases, and tissue oxygenation during apneas. However, if the sleep apneas continue for several years, carotid bodies may eventually get “desensitized” and become insensitive to hypoxia, leading to depressed hypoxic ventilatory sensitivity. Because the carotid bodies are not functional (i.e., insensitive to hypoxia), hypoxia associated with apneas may depress breathing (central hypoxic depression). Perhaps this may explain depressed hypoxic ventilatory sensitivity and elevated resting arterial P_{CO_{2}} seen in some of the patients with a long history of apneas. However, further studies are necessary to demonstrate whether carotid bodies get desensitized with extended exposures to intermittent hypoxia.

**CHF**

Patients with CHF exhibit periodic breathing, increased sympathetic nerve activity, augmented ventilatory response to hypoxia, and hypercapnia (38, 75). Brief hyperoxic exposure prevents periodic breathing in CHF subjects. Because hypoxia depresses carotid body activity, it has been suggested that CHF increases the gain of peripheral chemoreceptor reflex leading to instability of breathing (75). Carotid body reflexes were directly tested in an experimental model of CHF. Sun et al. (80) examined ventilatory and sympathetic nerve responses in conscious rabbits with a heart-pacing model of CHF. The development of CHF (after 3–4 wk of pacing) was characterized by enlarged hearts, attenuated cardiac contractility, and elevated central venous pressure. Baseline renal sympathetic nerve activity during normoxia was higher in CHF compared with control rabbits. The magnitude of increases in renal sympathetic nerve activity and minute ventilation elicited by isocapnic hypoxia was significantly greater in CHF than in control rabbits. Brief hyperoxic exposure (100% O_{2}) decreased renal sympathetic nerve activity in CHF but not in control rabbits, suggesting augmented peripheral chemoreceptor activity. In sharp contrast, the magnitude of increases in renal sympathetic nerve activity and minute ventilation by hyperoxic
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hypercapnia was nearly the same in both groups of animals, suggesting selective augmentation of peripheral chemoreflexes in experimental CHF. In a subsequent study, the same group of investigators (81) recorded carotid body activity in CHF rabbits. Baseline sensory discharge under normoxia and sensory response to graded hypoxia were significantly augmented in CHF compared with sham rabbits. Similar enhancement in hypoxic sensory response was also seen in ex vivo carotid body preparation, suggesting that the observed increases in sensory response were not secondary to cardiovascular changes. Endogenous nitric oxide (NO) generated by NO synthase isoforms exerts tonic inhibitory influence on carotid body activity (66). The following lines of evidence suggest that the enhanced sensory response associated with experimental CHF involves downregulation of NO synthases in the carotid body (81). These include 1) NO synthase inhibitor augmented baseline activity in control but not in CHF carotid body; 2) NO production during normoxia in the carotid body was markedly decreased in CHF but not in sham rabbits; and 3) NO synthase-positive nerve fibers within the carotid body are absent in CHF rabbits. These studies thus provide convincing evidence for chemoreceptor reflexes in CHF.

Hypertension

Patients with essential hypertension exhibit an augmented ventilatory response to hypoxia and increases in the sympathetic nerve activity (38, 85). Fukuda et al. (23) recorded carotid body sensory activity in normotensive and spontaneously hypertensive rats. These investigators found significant enhancement of carotid body sensory response to hypoxia in spontaneously hypertensive compared with normotensive rats, whereas sensory response to CO2 was nearly the same between both groups of animals. On the other hand, carotid body sensitivity to hypoxia was unaltered in renal hypertension (1). Therefore, changes in carotid body sensitivity appear to depend on the type of hypertension (i.e., essential vs. renal), although these studies demonstrate that certain forms of hypoxia enhance carotid body activity seen in hypertensive rats. Thus, changes in carotid body activity associated with experimental CHF involves downregulation of NO synthases in the carotid body (81). These include 1) NO synthase inhibitor augmented baseline activity in control but not in CHF carotid body; 2) NO production during normoxia in the carotid body was markedly decreased in CHF but not in sham rabbits; and 3) NO synthase-positive nerve fibers within the carotid body are absent in CHF rabbits. These studies thus provide convincing evidence for chemoreceptor reflexes in CHF.

Chemoreceptor Reflexes in Other Pathophysiological Situations

There are studies that demonstrate altered carotid body morphology in chronic obstructive pulmonary (31, 86) and acute respiratory distress syndrome (86) and in sudden infant death syndrome (29, 62, 63). However, functional consequences of the morphological changes in the carotid body in these diseases are not known.

In summary, we attempted to highlight the importance of peripheral chemoreceptors for maintaining O2 homeostasis in physiological and pathophysiological situations. Studies on experimental animals and human subjects show that carotid bodies are the primary sensors for eliciting ventilatory stimulation by hypoxia. However, in the chronic absence of carotid bodies, upregulation of noncarotid body chemoreceptors contributes to the maintenance of the hypoxic ventilatory response. The mechanisms associated with upregulation of other chemoreceptors, however, require further study. Although there is considerable evidence for the involvement of peripheral chemoreceptors in exercise-induced hyperventilation, altitude acclimatization, and pregnancy, cellular mechanisms associated with altered chemoreceptor function under these conditions are not known. Available evidence suggests enhanced chemoreceptor reflexes in early stages of recurrent apneas, CHF, and certain forms of hypertension. It is likely that chemoreceptors tend to maintain O2 homeostasis and act as a defense mechanism to prevent the progression of morbidity associated with these diseases.

REFERENCES


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