6.6 Control of Ventilation

Learning Objectives

- List the muscles of respiration
- Identify the origin of voluntary and involuntary controls of ventilation
- Define PRG and indicate its location and its effect on ventilation
- Define DRG and indicate its location and its influence on ventilation
- Define VRG and indicate its location and its influence on ventilation
- Describe the location and sensitivity of the peripheral chemosensors
- Describe the afferent nerves for the carotid bodies and aortic bodies
- Describe how pH, P_{CO_2}, and P_{O_2} affect the firing rates of chemosensors in the carotid and aortic bodies
- Describe the Hering—Breuer inflation reflex
- Describe the location of the central chemosensors
- Explain how the central chemosensors respond to plasma pH and P_{CO_2}
- Name the only chemosensor that responds to low P_{O_2}
- Explain how increased ventilation occurs during exercise

NERVES REGULATE BREATHING

The **phrenic nerve** is actually a pair of nerves, the right and left phrenic nerves, that activate contraction of the diaphragm that expands the thoracic cavity. Because the lungs are stuck to the thoracic cavity, this expands the lungs and thereby draws air into them. The cell bodies of the motor neurons that make up the phrenic nerve reside in a longitudinally oriented column in segments C3—C5 of the spinal cord. Initiation of action potentials in the **external intercostals** elevates and expands the rib cage, aiding inspiration. The cell bodies of the motor neurons that control the external intercostals form a column that extends the entire length of the thoracic spinal cord. Similarly, motor neurons that control the **internal intercostals**, which aid expiration, form a separate column. The **abdominal muscles** also aid expiration, and the cell bodies of their motor neurons are found in the lower thoracic and upper lumbar spinal cord segments. The locations of these are shown schematically in Figure 6.6.1.

These observations permit an obvious conclusion: ventilation requires the activation of muscles which is accomplished through motor neurons. Thus the generation of the basic rhythm of breathing and its regulation during activity such as swimming or singing or talking or eating or sleeping and during exercise must ultimately involve nerve centers that control these motor neurons.

CONTROL OF BREATHING INVOLVES VOLUNTARY AND INVOLUNTARY COMPONENTS

Everyday experience tells us that we can regulate our breathing to accomplish tasks such as swimming, singing, talking, and eating. This ability constitutes a voluntary component to control of ventilation. During sleep we continue to breathe without voluntary control. **Voluntary control arises from the cerebral cortex**, whereas **involuntary control arises from centers in the medulla and pons**. Both areas project to the same final pathway: the spinal motor neurons that control respiratory muscles. However, these dual control systems project to these motor neurons via different pathways (see Figure 6.6.2). Cutting through the brain stem above the pons in experimental animals removes all voluntary control and only automatic mechanisms in the brain stem drive ventilation.

THE BRAIN STEM CONTAINS A *PONTINE RESPIRATORY GROUP* IN THE PONS, AN *APNEUSTIC CENTER* IN THE LOWER PONS, AND *DORSAL AND VENTRAL RESPIRATORY GROUPS* IN THE MEDULLA

Part of the evidence for the contemporary model of ventilatory control arose from experiments in animals in which the brain stem was transected at different places (see Figure 6.6.3). These experiments indicated the existence of a **pontine respiratory group (PRG)** that switches off inspiration; an **apneustic center** in the middle pons that prevents the switch off of inspiration, and two more areas in the medulla, the **dorsal respiratory group (DRG)** and **ventral respiratory group (VRG)**. Further investigations have continued to use experimental animals as direct information from humans is scarce.

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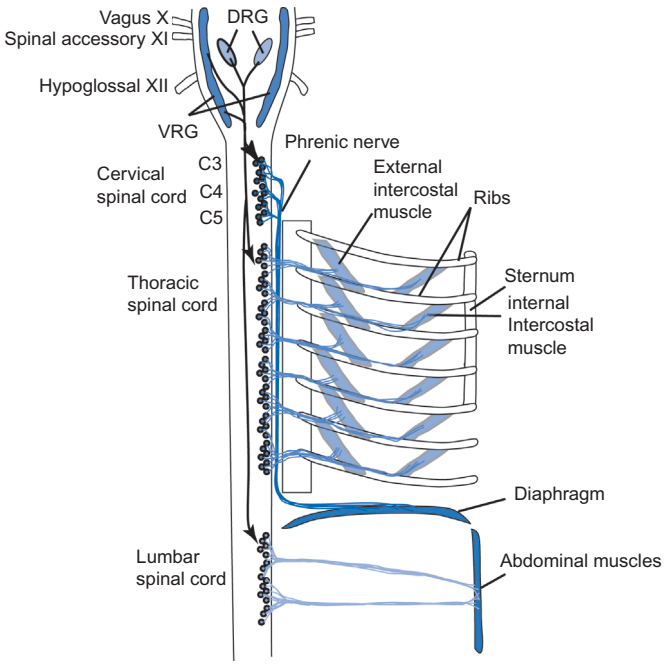

FIGURE 6.6.1 Location of the spinal motor neurons that control respiratory muscles. The cell bodies of motor neurons that activate the diaphragm are located in C3–C5. Their axons collect in the phrenic nerve. Cell bodies of motor neurons controlling the intercostal muscles are located in the thoracic spinal cord. The abdominal muscles are controlled by motor neurons whose cell bodies are in the lower thoracic and upper lumbar spinal cord. All of these motor neurons receive inputs from controlling centers in the medulla. The DRG is the dorsal respiratory group in the medulla; the VRG is the ventral respiratory group. *Adapted from M.P. Hlastala and A.J. Berger,* Physiology of Respiration, *Oxford University Press, 2001.*

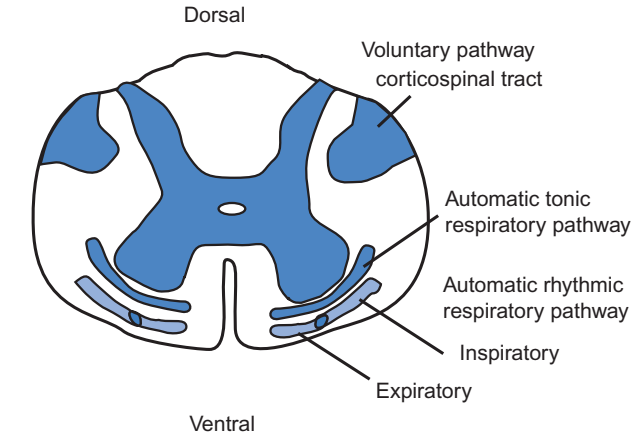

FIGURE 6.6.2 Location of descending pathways for the control of spinal respiratory motor neurons. The diagram shows a midcervical section of the spinal cord. The corticospinal tract in the dorsolateral cord contains axons of cells in higher centers. Descending automatic respiratory drive is carried in ventrolateral columns. Axons controlling expiratory motor neurons are situated medially, whereas those controlling inspiration are situated more laterally. The tonic involuntary pathway originates in the medial reticular formation of the medulla. *Redrawn from M.P. Hlastala and A.J. Berger,* Physiology of Respiration, *Oxford University Press, 2001.*

THE DRG RECEIVES A VARIETY OF INPUTS AND EXCITES INSPIRATORY MOTOR NEURONS

The DRG, located in the dorsal medial medulla, receives afferent signals over the **glossopharyngeal** and **vagus** nerves. These provide the DRG with sensory information from chemoreceptors in the carotid body and aortic body, as well as slowly and rapidly adapting stretch receptors in the lungs, and from C fiber endings in the lung. The DRG contains mainly neurons that directly excite motor neurons whose axons exit the spinal cord in the phrenic nerve to activate the diaphragm. These DRG neurons are called **I neurons**, for neurons that drive inspiration. These I neuron fibers cross the midline in the medulla. This is consistent with the general plan of the nervous system in which much sensory and motor information cross over to the contralateral side (see Figure 6.6.4). The DRG projects to the PRG and to the VRG. Thus the DRG tells the PRG and VRG that inspiration has begun at the same time that it begins.

THE VRG CONTAINS BOTH I AND E NEURONS

The VRG is located in the ventrolateral region of the medulla as shown in Figure 6.6.3. It has both inspiratory or **I neurons** that fire action potentials during the inspiratory phase of the respiratory cycle, and expiratory or **E neurons** that fire action potentials during the expiratory phase. I neurons predominate in the middle of the VRG, whereas E neurons are more abundant in both the rostral (toward the nose) and caudal (toward the tail) parts of the VRG. The I and E neurons are segregated in the spinal cord as well (see Figure 6.6.2). Both I and E neurons cross over the midline to project to the contralateral spinal motor neurons. Axons from I neurons cross rostrally, whereas the axons from E neurons cross more caudally. E neurons in the caudal VRG make monosynaptic contacts with expiratory internal intercostal motor neurons (see Figure 6.6.4).

I neurons from the intermediate VRG project contralaterally to descend the cord and make contact with spinal motor neurons. Axons from this part of the VRG also project to the contralateral VRG, making contact with both I and E areas.

The most rostral part of the VRG contains E neurons and is postulated to be the site of central pattern generation for the respiratory system. It sends inhibitory processes to the contralateral DRG and others to the ipsilateral caudal VRG, which contains other E neurons. The exact connectivity of these neurons is unknown. A specialized area, called the **pre-Botzinger complex (PBC)**, is located in the rostral part of the VRG and appears to be the "kernel" of respiratory rhythm generation.

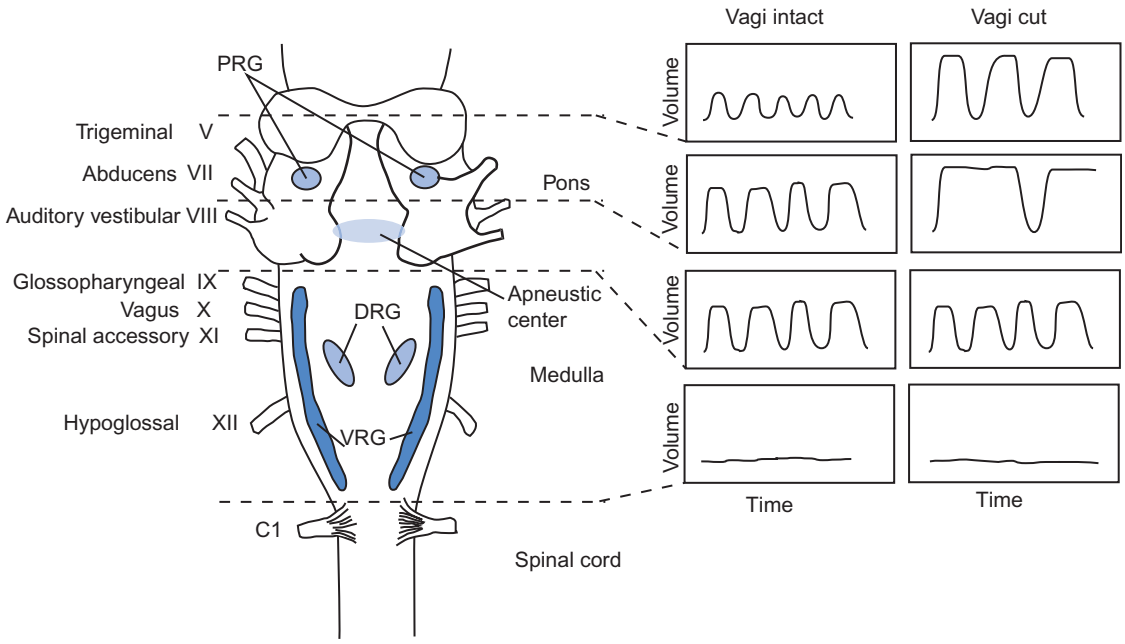

FIGURE 6.6.3 Effect of transections of the brain stem on respiratory patterns. The drawing shows a dorsal view of the brain stem after removal of the cerebellum. Transection above the pons removes voluntary control but respiration has a normal depth and rhythm. If the two vagus nerves are cut, inspiration is deeper than usual and the breathing frequency decreases. Thus the vagi supply sensory information that switches inspiration to expiration. Transection in the mid pons results in deeper inspiration with decreased frequency, suggesting that the transection removes a center that switches from inspiration to expiration. This center is the **PRG**, the **pontine respiratory group**. Section of the vagi with transection at mid pons results in apneusis, a breathing pattern consisting of long and deep inspirations punctuated with rapid expirations. Transection between medulla and pons with the vagi cut does not result in apneusis, suggesting there is a center in the lower pons that inhibits the switch from inspiration to expiration. This is the **apneustic center**, whose normal function remains unclear. Transection below the medulla removes all rhythmic breathing, indicating that the major sources of normal respiratory rhythm are located in the medulla. These are the **dorsal respiratory group (DRG)** and **ventral respiratory group (VRG)** of respiratory neurons.

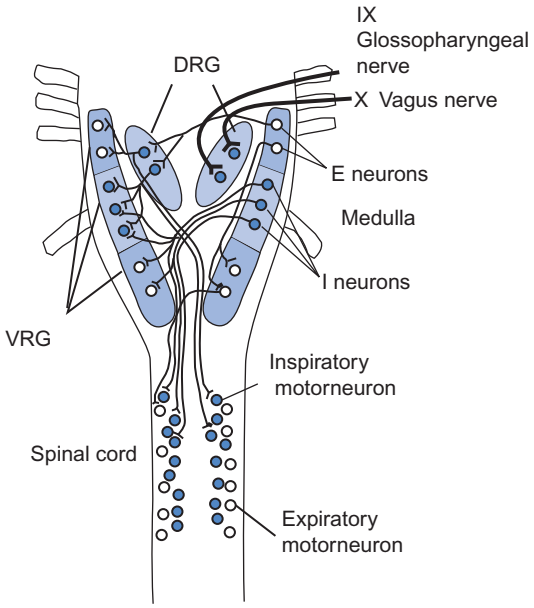

FIGURE 6.6.4 Connections between the DRG and VRG and their projections to the spinal motor neurons. Neurons that fire during inspiration (I neurons) are shown in dark; neurons that fire during expiration (E neurons) are light. The DRG contains predominantly I neurons that cross over and project onto spinal neurons that control inspiratory muscles. The DRG neurons also project to the ipsilateral VRG to both I and E neurons. The VRG has three sections. The most caudal and rostral parts of the VRG contain mainly E neurons, whereas the middle part contains I neurons. E neurons from the rostral VRG form inhibitory synapses on the contralateral DRG neurons and also form excitatory synapses on the ipsilateral caudal VRG E neurons. I neurons in the central VRG cross the midline and innervate spinal motor neurons for inspiratory muscles on the contralateral side. They also synapse on the contralateral I and E neurons of the VRG. Only one side of each connection is shown in the diagram. These connections are only a fraction of the total connections that occur between these structures.

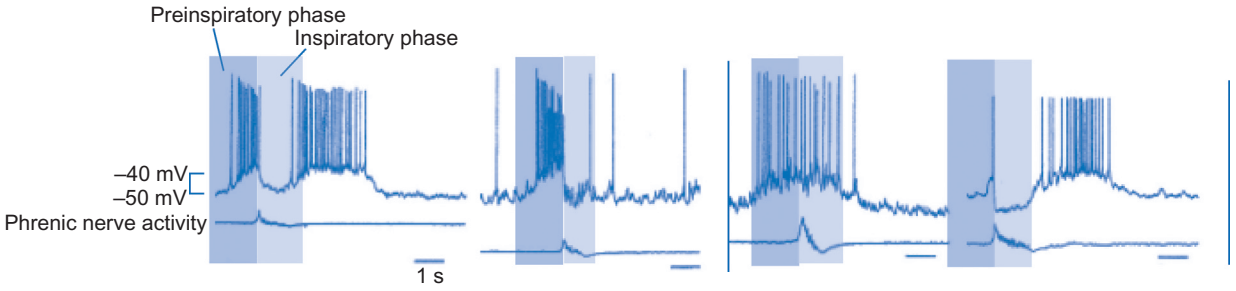

FIGURE 6.6.5 Responses of neurons classified as "pre-I" neurons. These neurons typically produce action potentials during the preinspiratory phase of respiration. They are generally inactive during the respiratory phase, but become variably active again during the postrespiratory phase. *From H. Onimura, A. Arata, and I. Homma, Neuronal mechanisms of respiratory rhythm generation: an approach using an in vitro preparation.* Jap. J. Physiol. *47:385–403 (1997).*

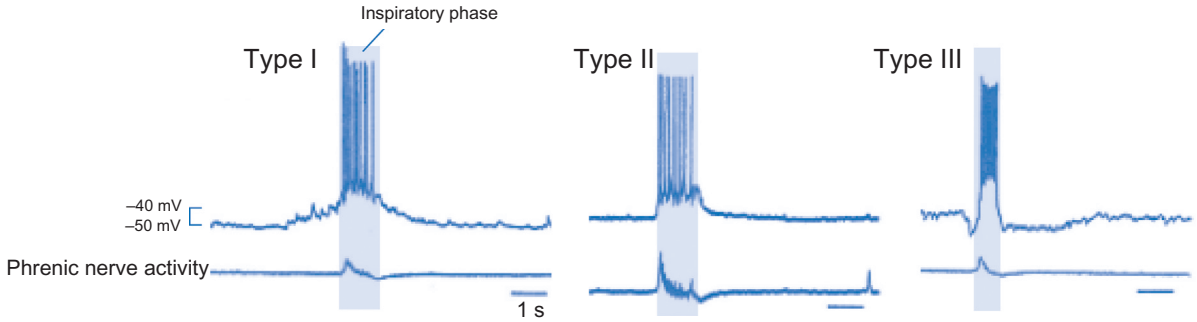

FIGURE 6.6.6 Responses of neurons classified as inspiratory or Insp neurons. These typically are active during the inspiratory phase of respiration and either show depolarizations around inspiration (Type I) or no postsynaptic potential (Type II) or hyperpolarizations (Type III). *From H. Onimura, A. Arata, and I. Homma, Neuronal mechanisms of respiratory rhythm generation: an approach using an in vitro preparation.* Jap. J. Physiol. *47:385–403 (1997).*

NEURONS IN THE VRG HAVE A MORE VARIED ACTIVITY THAN "EXPIRATORY" OR "INSPIRATORY"

Respiratory neurons have a more complicated electrical pattern than simply "inspiratory" or "expiratory." Electrical recordings reveal neurons that depolarize to form bursts of action potentials prior to the inspiratory drive along the phrenic nerve. These have been called "preinspiratory" (Pre-I) neurons. These Pre-I neurons are usually hyperpolarized during the inspiratory phase and initiate action potentials again after inspiratory drive is over. Thus these Pre-I neurons are biphasic. This biphasic pattern is variable, with about 20% of the Pre-I neurons showing no inhibition during the inspiratory phase (see Figure 6.6.5). Other neurons fire mainly during the inspiratory phase, called Inspiratory (Insp) neurons, and these can be divided into three subtypes based on their differing postsynaptic potentials during the pre- and postinspiratory phases (see Figure 6.6.6). Type I Insp neurons have gradual depolarization during the preinspiratory phase, and similar diminishing depolarizations during the postinspiratory phase, probably due to synaptic connections to pre-I cells. Type II Insp neurons lack such connections, and therefore lack the depolarizations in either the pre- or postinspiratory phase. Type III Insp neurons show hyperpolarizations during the pre- and postinspiratory phases.

DESPITE PROGRESS, THE NEURAL MECHANISM OF THE RESPIRATORY PATTERN REMAINS UNKNOWN

The whole point of determining the nerve centers that control respiration and their inhibitory and excitatory connections to other nerve centers is to produce a model of how the nervous system generates and modulates the respiratory rhythm. Unfortunately, the neural basis for the respiratory rhythm remains elusive despite the identification of the PRG, DRG, VRG, PBC, and some of their main connections (see Figure 6.6.4). Part of the difficulty lies in the complexity of multiple connections and inputs.

There appear to be two major contenders for the rhythm generator itself. The first are cellular pacemakers. These are neurons with voltage- and time-dependent channels that produce rhythmic behavior at the cellular level. Indeed, some neurons with promising characteristics have been identified in the PBC in the rostral VRG.

The second possibility is that rhythm generation is a system property that arises from interactions between neurons due to patterns of inhibition and excitation along with appropriate sensory input. It is clear, for example, that sensory input from the vagus nerves has profound effects on the respiratory patterns generated

by the brain stem. In the mature animal, experiments suggest that the respiratory rhythm does not originate from pacemaker cells, but it is a network property requiring interaction among neurons.

Despite this lack of a comprehensive neural model, there is more known about control of ventilation from peripheral sensors, which we will now discuss.

PERIPHERAL CHEMOSENSORS MODULATE RESPIRATION IN RESPONSE TO CHANGES IN $P_{a_{O_2}}$, P_{aCO_2}, AND pH

The peripheral sensory organs that detect changes in arterial P_{O_2}, P_{CO_2}, and pH are located in specialized areas called the **carotid bodies** and the **aortic bodies**. The carotid bodies dominate the signal—the aortic bodies are of secondary importance. The ventilatory response to lowering $P_{a_{O_2}}$ is almost exclusively determined by the carotid bodies. Their anatomic location is shown diagrammatically in Figure 6.6.7.

PERIPHERAL ARTERIAL CHEMOSENSORS INCREASE FIRING RATES WITH INCREASED $P_{a_{CO_2}}$, DECREASED PH, AND DECREASED $P_{a_{O_2}}$

The carotid chemosensors respond to changes in blood pH and blood gases by altering the frequency of action potentials transmitted by the glossopharyngeal nerve (cranial nerve IX) to the brain stem. At any pH, increasing $P_{a_{CO_2}}$ causes an increase in the firing rates of these chemosensors (see Figure 6.6.8). The results of Figure 6.6.8 also show that, at constant $P_{a_{CO_2}}$, increasing $[H^+]$ increases the rate of firing of the carotid chemosensors.

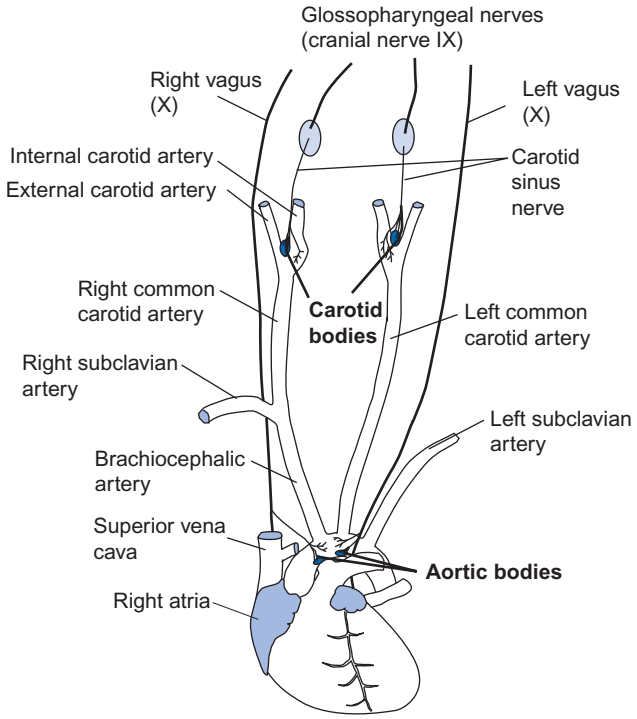

FIGURE 6.6.7 Anatomic location of the carotid and aortic bodies. The carotid bodies are located at the bifurcation of the common carotid to form the external and internal carotid arteries. These structures are about 5 mm long in the adult human and they are extremely well perfused with blood, some 20 mL per gram of tissue per minute. This is far above the metabolic needs of the tissue, so there is very little extraction of O_2 from the arterial blood. Thus the venous blood draining the carotid body has almost as high a P_{O_2} as the arterial blood. This high flow enables the carotid bodies to sense *arterial* gases and pH. The carotid body is innervated by the carotid sinus nerve, and sensory information travels to the brain stem through the **glossopharyngeal nerve**, cranial nerve IX. The aortic bodies are located in the aortic arch. They are innervated by the **vagus nerve**, cranial nerve X.

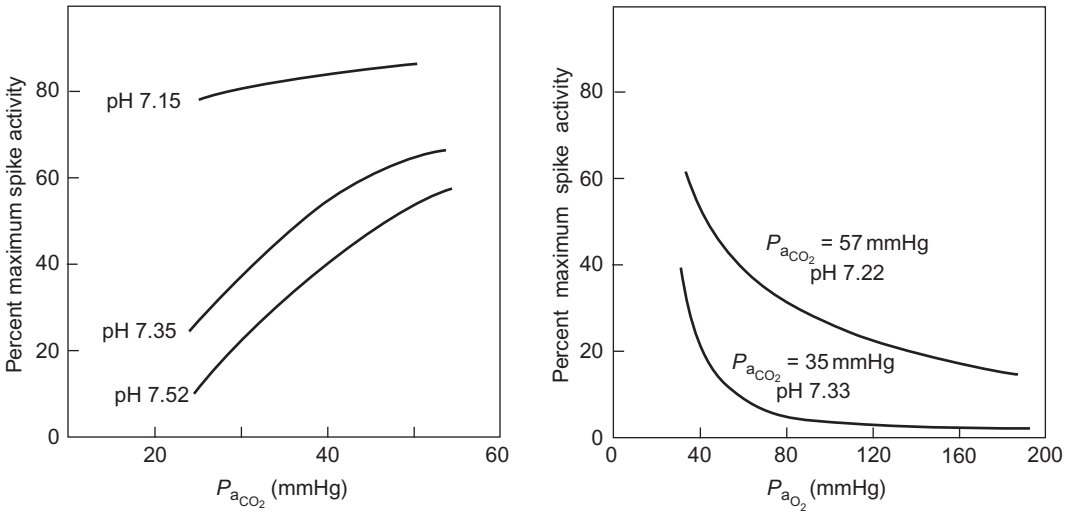

FIGURE 6.6.8 Response of the carotid chemoreceptors to pH, $P_{a_{CO_2}}$, and $P_{a_{O_2}}$. The response is measured as the frequency of action potentials. Increasing $P_{a_{CO_2}}$ increases the firing activity (left) at a constant pH, and decreasing pH increases firing activity at constant $P_{a_{CO_2}}$. Decreasing $P_{a_{O_2}}$ increases the firing rate (right) at constant pH and $P_{a_{CO_2}}$, but increasing $P_{a_{CO_2}}$ (with consequent acidemia) augments the response. Hypoxia (low $P_{a_{O_2}}$) does not stimulate the chemoreceptors until $P_{a_{O_2}}$ falls below about 60 mmHg. *Adapted from M.P. Hlastala and A.J. Berger,* Physiology of Respiration, *Oxford University Press, 2001.*

Decreasing $P_{a_{O_2}}$ below about 60 mmHg also stimulates the firing of carotid chemosensors. Note that this is arterial P_{O_2}, which normally is about 100 mmHg. Thus there must be a fairly drastic drop in blood $P_{a_{O_2}}$ before the peripheral chemoreceptors become activated. The data of Figure 6.6.8 indicate that these receptors are more sensitive to pH and $P_{a_{CO_2}}$ than they are to $P_{a_{O_2}}$.

PERIPHERAL CHEMOSENSORS FOR $P_{a_{O_2}}$ ARE MORE IMPORTANT THAN THOSE FOR $P_{a_{CO_2}}$

Changes in ventilation caused by **hypercapnia** (increased $P_{a_{CO_2}}$) are only slightly reduced when the sensory input from the carotid bodies is cut, indicating that there are other sensors for $P_{a_{CO_2}}$. On the other hand, **in humans the carotid bodies are the only sensors for** $P_{a_{O_2}}$ and the hyperventilation that accompanies low $P_{a_{O_2}}$ is entirely due to input from the carotid bodies.

THE VENTILATORY RESPONSE TO INCREASED CHEMORECEPTOR FIRING RATE IS INCREASED VENTILATION

The chemoreceptor input travels over the glossopharyngeal nerve and the vagus nerve to the brain stem where it makes synapses with neurons in the DRG. These neurons are I neurons, and so increased rates of firing from the chemoreceptors cause increased inspiratory activity and increased pulmonary ventilation. This system makes a complete negative-feedback loop: hypercapnia increases chemoreceptor firing rate that increases inspiratory neuronal activity that increases ventilation that tends to reduce $P_{a_{CO_2}}$ by removing more CO_2 to the atmosphere, thereby reducing the original signal of increased $P_{a_{CO_2}}$. Similarly, acidemia increases chemoreceptor firing rate, leading to increased ventilation and, by lowering $P_{a_{CO_2}}$, the pH tends to normal by respiratory compensation (see Chapter 6.5). When $P_{a_{O_2}}$ falls, the chemoreceptors increase their firing rate, which increases ventilation which tends to restore $P_{a_{O_2}}$ toward normal. These negative-feedback loops are shown schematically in Figure 6.6.9.

CENTRAL CHEMOSENSORS PROVIDE THE MAJOR RESPONSE TO CHANGES IN $P_{a_{CO_2}}$

Although the peripheral chemoreceptors respond to acidemia and hypercapnia by increasing their firing rate, surgical removal reduces the ventilatory response only by about 10%. Thus, 90% of the response is due to some other process. This process resides in chemosensors located in the ventral medulla. These chemosensory zones have been localized by a variety of techniques including lesioning, electrical stimulation, and focal application of chemicals. Three zones are located in the ventral medulla just beneath its surface, as shown in Figure 6.6.10.

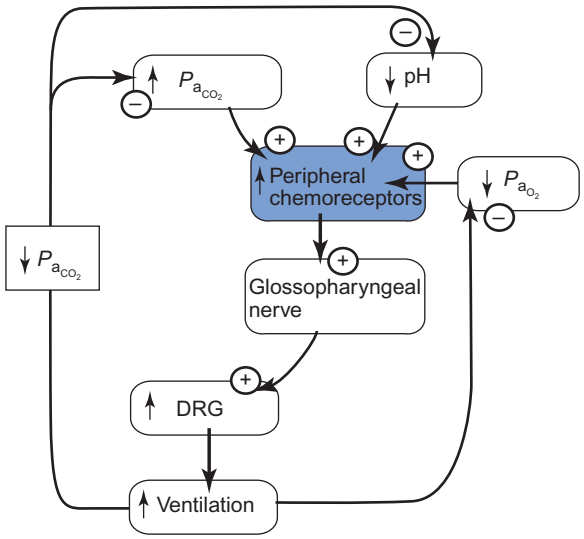

FIGURE 6.6.9 Negative-feedback loops in the control of ventilation by peripheral chemosensors. Chemosensors in the carotid bodies and aortic bodies respond to increased $P_{a_{CO_2}}$ by increasing their firing rate. This signal is carried to the DRG via the glossopharyngeal nerve and vagus nerve. These connect to inspiratory neurons in the DRG that increase the depth and frequency of breathing to increase pulmonary ventilation. This lowers the alveolar P_{CO_2} and hence arterial $P_{a_{CO_2}}$. Thus the loop acts to lower the original perturbation of hypercapnia. Similarly, decreased pH stimulates ventilation, which lowers $P_{a_{CO_2}}$ and therefore raises the pH toward normal. Decreased $P_{a_{O_2}}$ also stimulates the peripheral chemosensors, leading to increased ventilation and increased $P_{a_{O_2}}$.

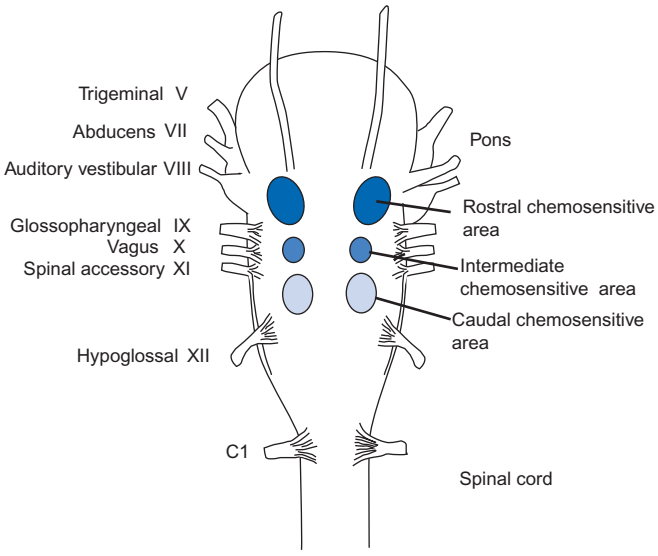

FIGURE 6.6.10 Location of the chemosensitive areas of the brain stem. The figure shows a ventral view of the brain stem. There appear to be three separate areas, one located rostrally, another caudally, and another intermediate between the two.

In experimental situations, the medulla can be perfused with solutions that vary the pH and P_{CO_2} separately by changing the $[HCO_3^-]$ according to the Henderson–Hasselbalch equation. In these cases, the hyperventilatory response (measured by the integrated response of the phrenic nerve) occurs when the pH is

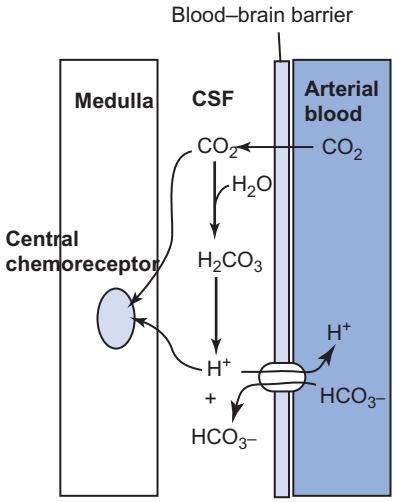

FIGURE 6.6.11 Connection between blood P_{CO_2} and CSF pH. CO_2 readily penetrates the blood–brain barrier whereas H^+ does not. During sustained acidosis, the CSF pH is initially depressed and then gradually returns to normal, suggesting the existence of some mechanism for regulating CSF pH independent of the pH of blood. Active pumping of HCO_3^- into the CSF (or of H^+ ions from CSF to blood) has been postulated as one possible mechanism for this regulation.

unchanged but P_{CO_2} is increased. It also occurs when the P_{CO_2} is unchanged and the pH is lowered. Thus it appears that the central chemoreceptors respond to either P_{CO_2} or the pH as independent stimuli. However, these experiments do not identify the stimulus at the surfaces of the central chemosensors.

The central chemoreceptors are functionally and structurally separated from blood by the **blood–brain barrier** (see Chapter 4.1). The interstitial fluid bathing the cells is separated from blood by a layer of cells which is composed of tightly joined **endothelial cells** and **astrocytes**. The **cerebrospinal fluid (CSF)** that fills the major brain cavities and the spaces between the meninges is made by **ependymal** cells that line these cavities but are especially prominent in the **choroid plexuses** within the ventricles of the brain. Ions such as H^+ and HCO_3^- do not easily cross the blood–brain barrier, whereas lipophilic materials such as CO_2 easily cross. Thus CO_2 in the blood crosses the blood–brain barrier and equilibrates with CO_2 in the CSF. There it hydrates to form carbonic acid, H_2CO_3, which then dissociates to form H^+ and HCO_3^-. Increasing blood $P_{a_{CO_2}}$ increases CSF P_{CO_2} which in turn increases CSF $[H^+]$ (see Figure 6.6.11). The chemoreceptors sense this decreased pH in the CSF and increase their firing rate, which in turn increases respiration. The cells that respond to changes in CSF composition have not yet been identified, and it is not yet clear whether they respond directly to local $[H^+]$, P_{CO_2}, or both.

THE BRAIN ADJUSTS THE $[HCO_3^-]$ OF THE CSF

Hypercapnia that causes a decreased pH of the CSF is followed by a gradual return of the CSF pH toward normal. Thus the brain possesses regulatory mechanisms that locally adjust disturbances in the CSF's pH. Nobody knows exactly how this is accomplished and several competing theories exist. The events depicted in Figure 6.6.11 are one way by which this regulation could occur. Changes in CSF $[HCO_3^-]$ occur slowly and the return to normal pH may take many hours or days. Ventilation may reflect differences in the sensory information provided by central and peripheral chemoreceptors.

VENTILATORY DRIVE INCREASES BY INTEGRATED RESPONSE TO ELEVATED $P_{a_{CO_2}}$, METABOLIC ACIDOSIS, OR HYPOXIA

HYPERCAPNIA STIMULATES VENTILATORY DRIVE

Acute increase in $P_{a_{CO_2}}$ decreases arterial blood pH. Both elevated $P_{a_{CO_2}}$ and decreased blood pH stimulate the peripheral chemoreceptors to increase ventilatory drive. The elevated CO_2 crosses the blood–brain barrier, acidifies the CSF, and excites the central chemoreceptors to increase ventilatory drive. So in the acute phase of hypercapnia, increased ventilatory drive derives from both peripheral and central chemoreceptors. The hypercapnia cannot remain in the face of increased ventilation unless there is some problem with gas exchange such as occurs in emphysema.

In the chronic phase of hypercapnia, blood pH returns toward normal and so only the elevated $P_{a_{CO_2}}$ remains to stimulate the peripheral chemoreceptors. Similarly, the CSF regulates its pH so that this component of central chemoreceptor stimulation is reduced. The result is a continued increased ventilatory drive but with greatly reduced magnitude.

METABOLIC ACIDOSIS INCREASES VENTILATORY DRIVE

Acute metabolic acidosis decreases the pH of the arterial blood and strongly stimulates the peripheral chemoreceptors to increase ventilatory drive. The increased ventilatory drive results in decreased $P_{a_{CO_2}}$ and subsequent rise in plasma pH. This respiratory compensation of the metabolic acidosis occurs relatively fast. Since H^+ penetrates the blood–brain barrier very slowly, the reduced $P_{a_{CO_2}}$ produces a paradoxical alkalinization of the CSF with a *decrease* in the stimulation of central chemoreceptors. Thus the overall ventilatory drive provided by the acidosis stimulating the peripheral chemoreceptors is blunted by the reduction in central chemoreceptor drive.

In the chronic phase of metabolic acidosis, there is a gradual return of the CSF from its initially alkalemic state to a normal pH. Thus the CSF has a normal pH with a reduced $P_{a_{CO_2}}$ caused by the increased ventilatory drive provided by peripheral chemoreceptors. Here the ventilatory drive provided by the central chemoreceptors returns toward normal (see Figure 6.6.12).

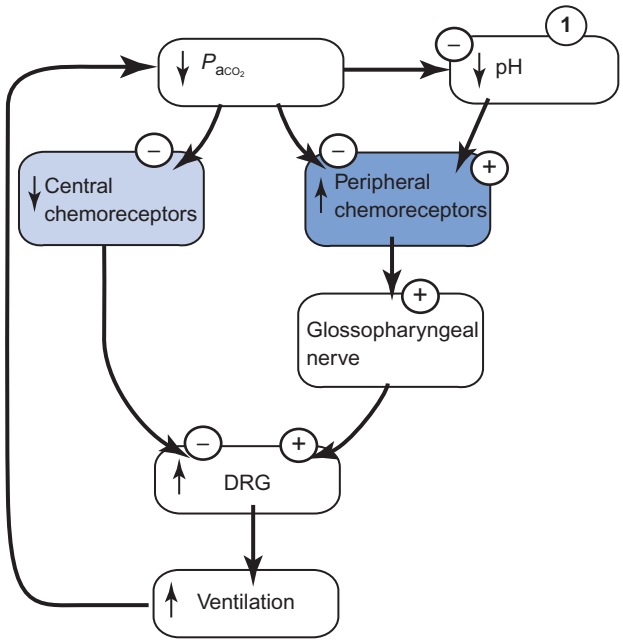

FIGURE 6.6.12 Feedback loops in ventilatory adjustment to metabolic acidosis. Start at 1 with the decreased pH. This stimulates the peripheral chemoreceptors, whose increased firing rates stimulate the DRG to increase ventilation. The increased ventilation decreases $P_{a_{CO_2}}$, which decreases its tonic stimulation of peripheral chemoreceptors. The decreased $P_{a_{CO_2}}$ also raises the pH because the excreted CO_2 originates from H^+ combining with HCO_3^-. The decreased $P_{a_{CO_2}}$ alkalinizes the CSF, thereby reducing central ventilatory drive. Thus the increased ventilatory drive provided by the decreased pH is suppressed by the resulting decreased $P_{a_{CO_2}}$.

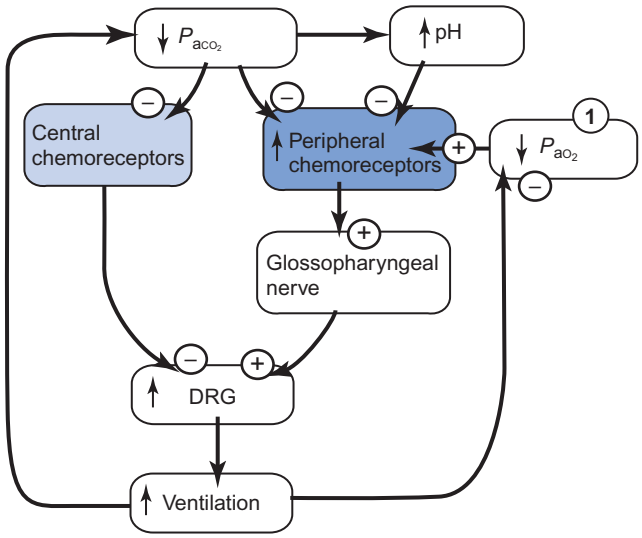

FIGURE 6.6.13 Feedback loops in ventilatory adjustment to hypoxia. Start at 1 with decreased arterial P_{O_2}. This stimulates only peripheral chemosensors to increase ventilatory drive. This reduces $P_{a_{CO_2}}$, which also increases plasma pH. Both the reduced $P_{a_{CO_2}}$ and alkaline blood reduce peripheral ventilatory drive. In addition, the reduced $P_{a_{CO_2}}$ reduces central ventilatory drive.

HYPOXIA INCREASES VENTILATORY DRIVE

Recall that the peripheral chemoreceptors are the only sensors for $P_{a_{O_2}}$. When $P_{a_{O_2}}$ falls below about 60 mmHg, the peripheral chemoreceptors are stimulated and ventilatory drive is increased. The increased ventilation causes $P_{a_{CO_2}}$ to fall, with a resulting alkalemia. The reduced $P_{a_{CO_2}}$ also alkalinizes the CSF, which reduces the ventilatory drive provided by the central chemoreceptors. The result is an attenuation of the ventilation stimulated by the peripheral chemoreceptors. This type of response would be seen by persons ascending to an altitude of about 3000 m (10,000 ft) where the $P_{I_{O_2}}$ is about 100 mmHg and $P_{a_{O_2}}$ is about 60 mmHg (see Figure 6.6.13).

After a few days at altitude, ventilation increases further. This is called **ventilatory acclimatization**. A progressive return of the CSF from alkaline to normal pH could explain this acclimatization, but the evidence does not support this mechanism. Because ventilatory acclimatization is ablated by removal of the peripheral chemoreceptors, it may be due to time-dependent changes in the sensitivity of the peripheral chemoreceptors.

Additional adaptations occur in persons who stay at altitude. Hypoxia stimulates secretion of **erythropoietin**, a glycoprotein hormone made in the kidneys. Erythropoietin stimulates the differentiation of uncommitted stem cells to begin forming erythrocytes. Thus hypoxia leads eventually to an increase in the number of circulating red blood cells, which increases the hematocrit and the hemoglobin concentration in blood, leading to increased O_2 content at any $P_{a_{O_2}}$. This condition is called **polycythemia**. Other adaptations to altitude are increased levels of 2,3-DPG in the blood and a persistent hypocapnic alkalosis. The increased level of 2,3-DPG shifts the O_2 dissociation curve to the right, while the hypocapnic alkalosis shifts the curve to the left. Up to an altitude of about 4250 m (14,000 ft) the result is an O_2 dissociation curve close to that at sea level. At extreme altitudes, the left shift due to alkalemia wins out.

AIRWAY AND LUNG MECHANORECEPTORS ALTER BREATHING PATTERNS

Sensory receptors are found in a variety of places throughout the respiratory system and are responsible for a wide variety of behaviors. These include the following:

- **Sneezing**: Mechanical stimulation of the nasal passage results in the sneeze reflex, consisting of a strong inspiration followed by a rapid expiration with partially closed airways to increase airflow velocity. The reflex clears foreign material from the passages.
- **The diving reflex**: Water in the nose elicits a complex series of respiratory and cardiovascular responses including cessation of respiration, closure of the larynx, bronchoconstriction, bradycardia, and vasoconstriction of many vascular beds except those of the brain and heart.

- **The aspiration reflex**: Mechanoreceptors in the epipharynx initiates a series of strong, brief inspirations that dislodge materials from the epipharynx into the pharynx where they can be coughed up or swallowed.
- **The swallowing reflex**: Adult humans cannot breathe and swallow at the same time. Receptors in the pharynx cause cessation of respiration, closure of the larynx, and coordinated muscular contractions that move material from the oral cavity into the esophagus.
- **Cough reflexes**: Rapidly adapting receptors in the airway epithelia respond both to mechanical deformation and chemical irritation. These receptors initiate reflexes that include coughing, mucus secretion, and bronchoconstriction. All of these actions have the common theme of removing the offending irritant. Coughing creates a high velocity of airflow that helps eliminate foreign matter. Increasing mucus secretion helps trap the foreign matter. Bronchoconstriction decreases the diameter of the airways and therefore increases the velocity of airflow produced by the cough, so that foreign matter can be more easily expelled.
- **The Hering–Breuer inflation reflex**: The lower airways contain slowly adapting stretch receptors. Afferent sensory information from these stretch receptors travels over the vagus nerve to the brain stem where it inhibits inspiration by stimulating the neurons in the PRG. This is the Hering–Breuer inflation reflex. Inflation of the lungs stimulates the stretch receptors, which reflexly inhibit further inflation.
- **The pulmonary chemoreflex**: In addition to stretch receptors, the vagus nerve carries sensory inputs from C fibers, which are unmyelinated nerves with slow conduction velocities on the order of 2.5 m s^{-1}. C fibers in the bronchi appear to respond mainly to stretch whereas those fibers near the capillaries respond to exogenous and endogenous chemicals including **capsaicin**, the irritant in red pepper, **histamine**, **bradykinin**, **serotonin**, and **prostaglandins**. These chemicals elicit the pulmonary chemoreflex that includes apnea, bradycardia, and hypotension that is immediately followed by rapid, shallow breathing (tachypnea).

INCREASED RESPIRATION DURING EXERCISE MAY BE NEURAL AND MAY INVOLVE LEARNING

Everyday experience tells us that exertion is accompanied by increased pulmonary ventilation. What regulates ventilation during exercise? Exercise increases O_2 consumption, CO_2 production, and H^+ generation from metabolic acids such as lactic acid, acetoacetic acid, and β-hydroxybutyric acid. These changes would reduce $P_{a_{O_2}}$, raise $P_{a_{CO_2}}$, and produce acidemia. All of these would lead to increased ventilatory drive. However, none of these are altered during moderate exercise. Respiratory adjustments are so precise that $P_{a_{O_2}}$, $P_{a_{CO_2}}$, and blood pH are perfectly normal. At higher work rates, pH and $[HCO_3^-]$ may actually fall.

Passive movements of the limbs of experimental animals increase ventilation; direct stimulation of muscles through their nerves also stimulates ventilation; blockade of the sensory afferents from the muscles blocks the effect. Muscle mechanoreceptors and nociceptors make the largest contribution to the hyperpnea of exercise. These results suggest that muscles and joints notify the respiratory centers about their activity through sensory afferents, thereby stimulating ventilation.

Stimulation of motor systems in paralyzed animals can elicit ventilatory drive similarly to exercise. This suggests that the motor systems that drive muscles send collaterals to the respiratory system to simultaneously drive ventilation. This is a **feedforward** mechanism in which the motor system anticipates the respiratory demands of its commands and adjusts ventilation in advance of those demands rather than waiting for discrepancies of respiratory gases or pH to stimulate ventilation.

Another possible explanation for exercise hyperpnea is altered sensitivity of the central controllers to input from the peripheral and central chemoreceptors. Feedforward input from motor systems or from muscle afferents could alter the response of the brain stem respiratory neurons so that the same input from the chemoreceptors produces a larger ventilatory drive.

The respiratory response to exercise may be in part conditioned by previous bouts of exercise. The observation is that exercise involves an error-free adjustment of ventilation so that blood gases and pH are normal during exercise of varying intensities. A negative-feedback mechanism can achieve zero error only by having an infinite gain. Real negative-feedback systems ought to have residual error that drives the increased ventilation. In principle, the brain could learn to titrate respiration according to muscle afferent information or output from the motor cortex so as to prevent blood gas abnormalities. In this hypothesis, each bout of exercise teaches the nervous system how much ventilation is necessary to prevent disorders of blood gases or pH with each increment in intensity of exercise.

Clinical Applications: Sleep Apnea

Absence of airflow for 10 s or longer is **apnea**; reduction in tidal volume between 50% and 75% for at least 10 s is hypopnea. Both apnea and hypopnea that occur during sleep can be classified as **central**, **obstructive**, or **mixed**. Central apnea is caused by reduced respiratory effort, whereas obstructive apnea involves persistent effort during the period of the apnea. Mixed apneas begin with a central component that is followed by an obstructive component. Sleep apnea is defined as cessation of airflow for 10 s or longer with a frequency of at least 15 episodes per hour. Normal young adults typically have up to five apneas per hour during sleep.

Obstructive sleep apnea, OSA, is predominantly a male problem, affecting 10 times as many men as women, afflicting some 2–4% of the general population. Nearly all persons with OSA snore loudly and most complain of daytime sleepiness because their apnea wakes them repetitively during the night. The cause is generally airway obstruction in the oropharynx related in part to relaxation of the tongue and pharynx during sleep. The majority of persons with OSA are overweight. Increasing body weight positively correlates with pharyngeal resistance and weight reduction generally improves the condition.

Weight reduction in persons with OSA often causes significant clinical improvement. Since most people with OSA experience sleep apneas in the supine position, sleep posture modification often improves the condition. Antidepressant drugs such as the tricyclic antidepressants reduce REM sleep, which is the stage of sleep most often associated with OSA. A tongue-retaining orthodontic appliance moves the tongue forward, thereby improving the opening of the pharyngeal airway. Supplemental oxygen or nocturnal ventilation by tracheostomy tube or face mask eliminates nocturnal hypoxemia and hypercapnia. For patients who have tried these or other methods and have dangerous OSA, surgical remedies may help. These include tracheostomy, uvulopalatopharyngioplasty, in which soft tissues of the soft palate, uvula, and posterior lateral pharyngeal wall is removed, and removal of the tonsils or adenoids.

SUMMARY

Ventilation of the lungs is controlled by the central nervous system. Voluntary control arises from the cerebral cortex, and involuntary control arises from the medulla and pons. These send inspiratory signals out to the diaphragm over the phrenic nerve, arising from C3–C5 spinal segments, and to the internal intercostals over thoracic segments. The pons contains a PRG that switches off inspiration and an apneustic center in the lower pons that sends signals to prevent switching off of inspiration. Sensory information coming into the medulla along the vagus nerves also helps switch off inspiration. The medulla contains DRG and VRG. The DRG contains primarily inspiratory neurons that fire action potentials during inspiration. The DRG receives sensory information from chemoreceptors in the carotid body over the glossopharyngeal nerve (CN IX) and from the aortic bodies over the vagus nerve (CN X). The VRG contains both inspiratory and expiratory neurons. A region in the rostral VRG may be the origin of the respiratory rhythm. There are multiple connections among the DRG, VRG, and spinal motor neurons that drive the respiratory muscles.

The peripheral chemoreceptors respond to $P_{a_{O_2}}$, $P_{a_{CO_2}}$, and pH. Increasing $P_{a_{CO_2}}$ or decreasing pH increases the frequency of action potentials of the peripheral chemoreceptors, which in turn increases ventilation by stimulating the DRG. The peripheral chemoreceptors are the only sensors for $P_{a_{O_2}}$. The ventral medulla contains central chemoreceptors that respond to the pH of the CSF. Metabolic acids and H^+ itself cannot easily cross the blood–brain barrier, whereas CO_2 easily crosses. Thus elevated $P_{a_{CO_2}}$ acidifies the CSF, causing increased ventilation. The CSF possesses mechanisms to regulate its pH independently of blood. In chronic conditions, the ventilatory drive provided by CSF acidosis gradually disappears, so that only the peripheral chemoreceptors drive ventilation. Increased ventilation caused by hypoxemia, resulting from ascent to altitude, e.g., decreases $P_{a_{CO_2}}$, which alkalinizes the CSF. This reduces the central drive for ventilation. After a few days at altitude the ventilatory drives increase further. In metabolic acidosis, the decreased pH increases ventilation due to excitation of the peripheral chemoreceptors. The increased ventilation lowers $P_{a_{CO_2}}$, which alkalinizes the CSF and reduces central chemoreceptor-driven ventilation.

REVIEW QUESTIONS

1. The actor Christopher Reeve suffered a high cervical spinal cord injury after falling while horseback riding. What is the consequence of this injury with respect to the control of breathing?
2. In metabolic acidosis, trace the signal from the peripheral chemoreceptor to its final effect on ventilation. Using the alveolar ventilation equation, predict in what direction this alters alveolar P_{CO_2}. In what direction does this alter arterial P_{CO_2}? Using the Henderson–Hasselbalch equation, predict the effect of this change on plasma pH. How does the change in arterial P_{CO_2} affect CSF pH? What effect does this have on central ventilatory drive?
3. Repeat review question 2 for metabolic alkalosis.
4. Why does the acute ventilatory response to metabolic acidosis differ from the chronic response?
5. For involuntary control of ventilation, cutting the two vagus nerves produces deeper ventilation at lower frequency (see Figure 6.6.3, top right trace). Why?
6. What provides increased ventilatory drive during exercise?