Section Three: Chapter 19: Respiratory Control

The Control of Ventilation

Ventilation is a complex interplay of multiple brain and body regions signaling muscles of ventilation to maintain homeostasis. The control of ventilation is thought to be seated in two primary regions of the brain that regulate breathing patterns and respond to input from sensory neurons monitoring the entire system. The two prominent brain regions are the **Medulla Oblongata** and the **Pons** (see **Fig. 19.1** below). The actions of these regions typically result in a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of $\mathbf{O_2}$ and adequately removal and balancing of $\mathbf{CO_2}$.

Other regions across the entire body can modify breathing. These include the cerebral cortex, limbic system, hypothalamus, pain perception, body position and body movement, etc. (see below). However it is usually considered to be the medulla and the pons that are the primary controllers of the rhythmic pace of breathing, the fine tuning, and the protective responses to prevent damage or injury to the lungs.

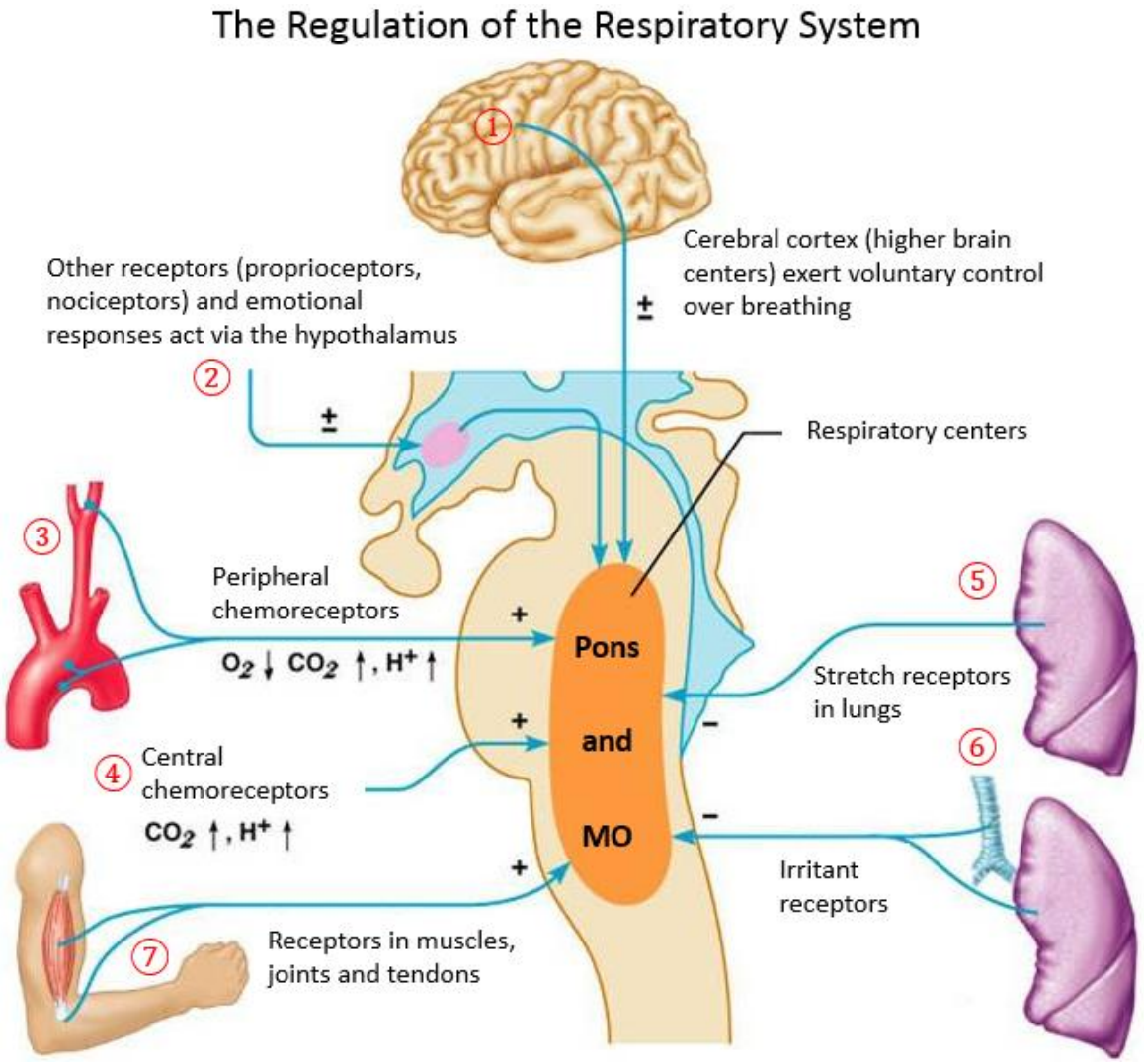

Figure 19.1 The myriad of influences that regulate the respiratory system are shown here. They range from the higher center of the brain (①and ②), the chemistry of the blood and cerebrospinal fluid (③ and ④), within the lungs and airways (⑤ and ⑥) and from peripheral tissues involved in body movement (⑦).

Ventilation Control Centers

As indicated, the two primary regions in the brain that regulate breathing are the **medulla oblongata** and the **pons**. In terms of the control of ventilation, it is a complex interplay of multiple regions in the brain that signal the muscles used in pulmonary ventilation. The result is typically a rhythmic, consistent ventilation rate that provides the body with sufficient amounts of O_2, while adequately removing and balancing the CO_2 levels.

As seen in **Fig. 19.1**, other regions of the brain and body can modify breathing due to changes in various states, but it is the respiratory control centers in the brain stem, the medulla oblongata and the pons, that control the rhythmic pace of breathing, the fine tuning of breathing and the protective responses that prevent damage or injury to the lungs. The focus will primarily be on these two regions, though the other factors will also be discussed.

1. The Medulla Oblongata and Respiration

The medulla oblongata (MO) contains the **dorsal respiratory group (DRG)** and the **ventral respiratory group (VRG)**. Which work in concert to establish and maintain rhythmic breathing.

a) Dorsal Respiratory Group (**DRG**):
The **DRG** is involved in maintaining **continuous rhythm breathing** by stimulating the **diaphragm** and **intercostal** muscles to contract which results in inspiration. When the neurons in the DRG stop firing, the primary muscles of inspiration relax. Due to the elasticity of the lung tissue, this results in expiration in eupnea, that is, there are no muscle contractions needed for exhaling air during quiet breathing.

b) Ventral Respiratory Group (**VRG**):
The **VRG** is involved in **forced breathing** (V as in 'vroom'). These neurons in the VRG stimulate the additional accessory muscles that are required for forced breathing, recruiting them to contract which results in forced inspiration.

Form the previous section on muscles of ventilation an example of these muscles is the **sternocleidomastoid** and the **scalenes** muscles to elongate the thoracic cage. The VRG also stimulates muscles involved in forced expiration to contract, those being the **abdominal** muscles.

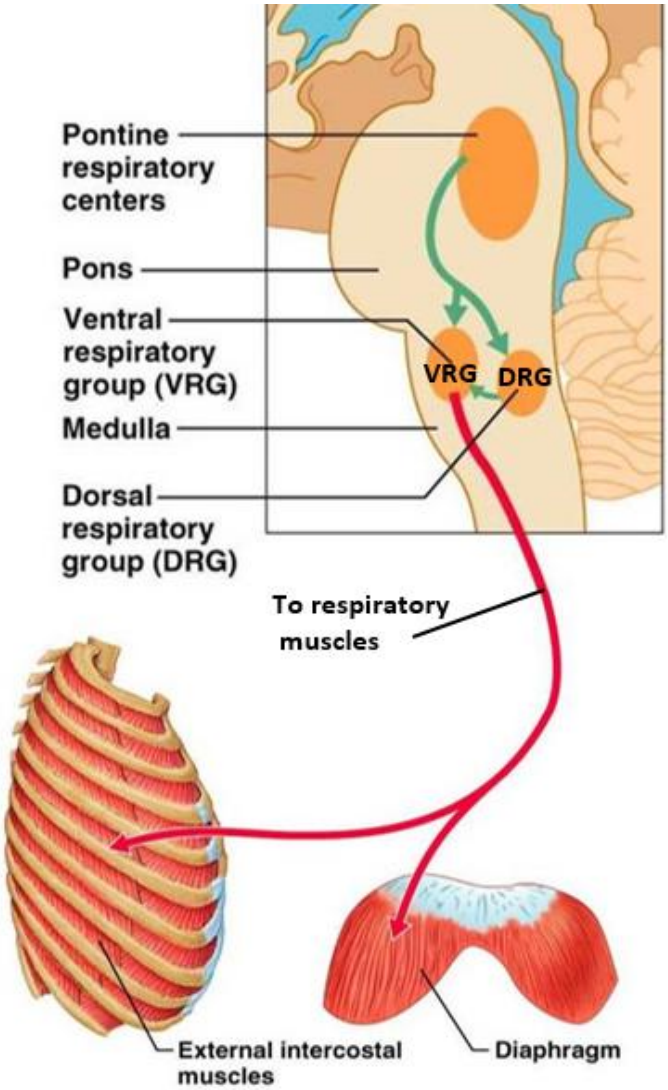

Figure 19.2 The diagram shows that how the dorsal respiratory group (DRG) and the ventral respiratory group (VRG) integrate information from the other centers and also interact, then send signals to the respiratory muscles.

2. The Pons (*Pontine* respiratory centers) and Respiration

The pontine respiratory group (in the pons) consists of two centers; the **apneustic center** and the **pneumotaxic center**, see **Fig. 19.3** below.

a) The **apneustic center** of pons is cluster of nerve cell bodies that sends signals to the DRG in the MO and acts to delay the off switch that signals the end of a typical inspiration. It controls the intensity of breathing, wherein it stimulates and prolongs inspiration, thus controlling the **depth of inspiration**, particularly for deep breathing.

b) The **pneumotaxic center** is a network of neurons that *inhibits activity of the* apneustic and *the DRG* (inspiratory center), allowing relaxation after inspiration, and thus controlling the overall rate and preventing the over inflation of the lungs.

The pneumotaxic center can be viewed as antagonistic to the apneustic center. This center sets the limit to over inflation of lung and receives its information from **mechanoreceptors** in lung tissue that detects excessive stretching.

These stretch receptors are found on walls of bronchi and bronchioles and are triggered during large inspirations. They signal the activation of the pneumotaxic center that will then inhibit apneustic center to prevent overinflating the lungs.

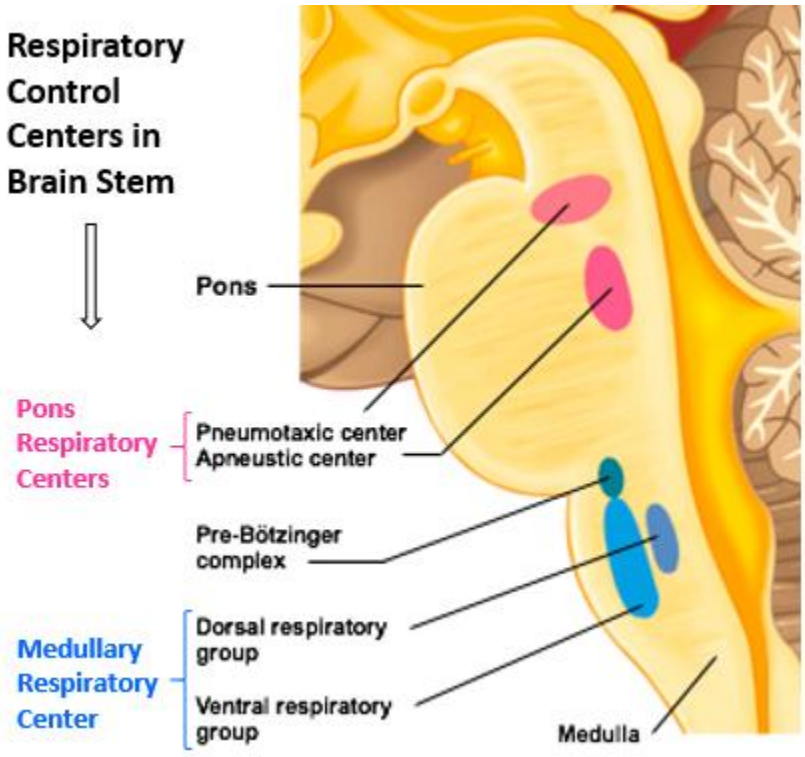

Figure 19.3 This diagram highlights the location and arrangement of respiratory control centers in the brain stem. The two main centers in the pons and medulla oblongata have groups within that integrate sensory information.

Factors that Affect the Rate and Depth of Respiration

The respiratory rate and the depth of inspiration are regulated by the **medulla oblongata** and the **pons**; however, these regions of the brain work in response to **systemic stimuli**. Many systemic factors have a role in integrating with the central nervous system to regulate pulmonary ventilation.

The Receptors of the Respiratory System

It is the sensory receptors that detect most of the changes that occur in our body, and sensory receptors are a key part in the regulation of the respiratory system.

Mechanoreceptors

Mechanoreceptors, or stretch receptors, are present throughout the entire respiratory tract. They are triggered by the physical distention of the tissue they are embedded in. They relay information to the CNS in the respiratory network of the brainstem regarding the mechanical status of the airways, lungs and the chest, and operating in feedback loops help regulate the control of breathing and to initiate protective reflexes inhibiting over inflation of the lungs and coughing to expel irritants in the airways.

The **pulmonary stretch receptors** are mechanoreceptors found in the lung tissue. When the lung expands, the receptors initiate the **Hering-Breuer inflation reflex**. The slowly adapting pulmonary stretch receptors have large myelinated fibers and are located in the larger regions of the airways, as they are situated in the **smooth muscles** of the respiratory tract. In addition, where there is an increased firing from the stretch receptors it stimulates an increased production of pulmonary surfactant. This helps to make the lung more compliant and expand more easily. An increase in pulmonary stretch receptor activity leads to an elevation of heart rate (tachycardia).

The **Hering–Breuer reflex** reduces the respiratory rate. It is triggered to prevent the over-inflation of the lung. This response involves the **vagus nerve** (recall this is the prominent nerve of the Parasympathetic division) which relays the signal to the **apneustic center** (in the pons) and the **DRG** (in MO). As a result, the inspiratory center is inhibited directly and the apneustic center is inhibited by the pneumotaxic center. This inhibits further inspiration and triggers expiration.

Mechanoreceptors in the lungs and airways have both **myelinated** and **unmyelinated nerve fibers**, which enter the brain mainly via **glossopharyngeal** and **vagus** nerves and terminate in the nucleus of the solitary tract, or the nucleus tractus solitarii (**NTS**).

The NST a major sensory nucleus is located in the dorsal medulla and is the first relay station for general visceral (organ) and taste sensations brought into the CNS via cranial nerves. This region has a critical role in the initiation and integration of a wide variety of reflexes regulating cardiovascular function, controlling respiration, and gastrointestinal motility.

Chemoreceptors

Peripheral and central chemoreceptors function to regulate respiratory activity and operate as a vital component for maintaining arterial blood P_{O2}, P_{CO2}, and pH within proper physiological ranges. As mentioned earlier, the primary regulator that stimulates the medulla oblongata and pons to control respiration is the partial pressure of CO_2 in the blood and cerebrospinal fluid (CSF). The concentrations and partial pressures of substances, including dissolved gases, are detected by **chemoreceptors**. The two types of respiratory chemoreceptors in the body are **peripheral** chemoreceptors and **central** chemoreceptors.

Peripheral Chemoreceptors

These are located in blood vessels in the periphery of the body, namely in the **carotid arteries** (blood supply to brain) and **aortic arch** (blood supply to body). These receptors are specialized to detect changes in blood chemistry of the following elements, and are most sensitive in this order:

1) P_{CO2} levels in arterial blood
2) pH of arterial blood
3) P_{O2} levels in arterial blood

The peripheral chemoreceptors are selectively responsive to **changes in the partial pressures of arterial O_2 and CO_2, and arterial p H**. Because they do not respond to changes in the O_2 or CO_2 content, a decrease in hemoglobin (anemia) does not increase breathing.

Peripheral chemoreceptors (carotid and aortic bodies) **detect changes in arterial blood oxygen and initiate reflexes** that are important for maintaining homeostasis during hypoxemia.

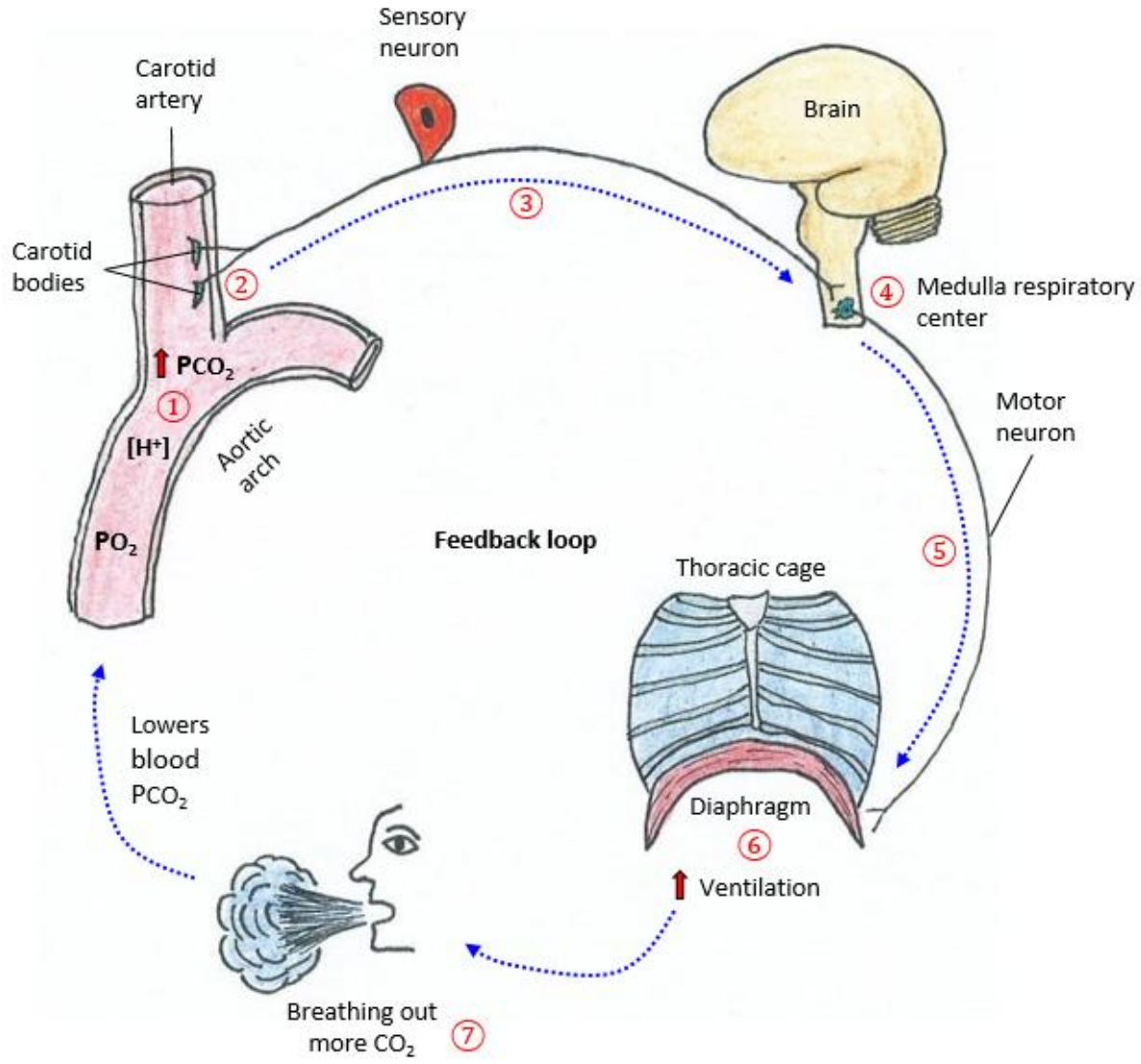

Figure 19.4 Displayed above is a feedback loop for homeostatically regulating breathing. The stimulus ① an increase in PCO_2 in arterial blood the receptors ② are carotid bodies that detect this change, the sensory pathway ③ takes this information to the integration center ④ the medulla oblongata, which then sends a signal via the motor pathway ⑤ to the effector ⑥ the diaphragm, which causes an increase in ventilation, which lowers PCO_2 ⑦.

Here is another example of the feedback loop for the respiratory system and blood chemistry regulation. Can you identify each element of the loop as numbered? What kind of feedback is it?

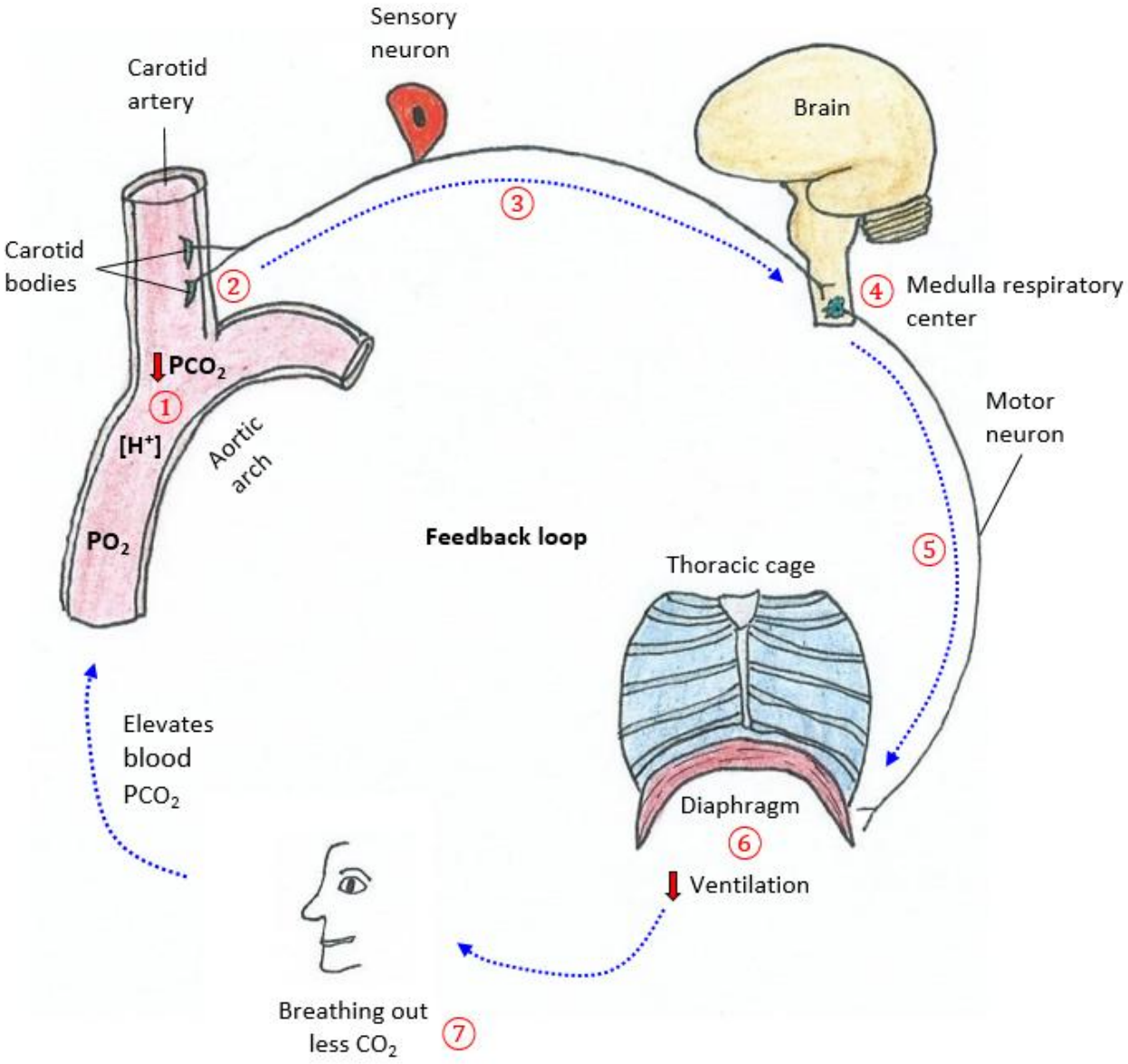

Figure 19.5 This breathing feedback loop is now dealing with the stimulus ① of a decrease in PCO_2 in arterial blood. Read through the numbered loop in sequential order and as practice describe the sequence of events and the outcome that will occur as a consequence of this feedback loop.

Questions Regarding the loop above in **Fig. 19.5**:

1. What is the stimulus that starts the loop?
2. What is the effector tissue and how does it respond?
3. What is the outcome of the effector tissue response?
4. Why would this response make sense in terms of physiology?

Answers in Appendix B.

Central Chemoreceptors

The **central chemoreceptors** are specialized receptors located in the brain (mostly the MO) that detect changes in CO_2 and H^+ in **cerebrospinal fluid** (**CSF**). Any significant changes here will signal the respiration centers of the brain to change in response to the current circumstance.

There is a little more to the story. The blood vessels of the brain have an additional protective and restrictive barrier around them, remember? It is called the **Blood Brain Barrier** (BBB) and is created by the astrocyte glia cells. What we need to know to understand how the central chemoreceptors work is that CO_2 can pass through this barrier (it's small, non-polar and not changed) and that H^+ (hydrogen ions or protons) cannot pass through this barrier (it is charged).

The Bicarbonate Buffer System

From our knowledge of the Bicarbonate Buffer System, we know that increases in CO_2 levels lead to increases levels of H^+ which will decrease the surrounding pH. As it turns out, it is actually changes in $[H^+]$ in the CSF that **triggers the central chemoreceptors**, this in turn signals the respiratory centers to change activity.

Why are these receptors sensitive to $[H^+]$ and not to CO_2 in the CSF? Simply put, it is because the H^+ cannot cross the BBB. If CO_2 is elevated in both arterial blood and the CSF, then even though the CO_2 can pass thru the BBB, there is no gradient for it to move from the CSF into the blood vessel, as both are elevated. This arrangement seems to have necessitated the signal for changes breathing to be **H^+** in the CSF since it cannot leave the brain if it becomes elevated (or decreased) and thus a reliable signal.

As the CSF experiences elevated CO_2 it continues to build up and pushes the bicarbonate buffer equation in the **forward direction**, making more H^+ inside the brain. As mentioned above, since these H^+ cannot move across the barrier into the blood vessel, it creates **more acidic conditions**, thus it is a powerful signal to the respiratory centers to change respiration in order to maintain homeostasis.

In the case of increases in H^+, this triggers **increased ventilation**. This causes more CO_2 to be exhaled, lowering arterial CO_2 levels, and this allows CO_2 to leave the CSF by moving into arterial blood (down its partial pressure gradient), which shifts the bicarbonate buffer in the reverse direction because of the reduction in CO_2 (law of mass action) and this **lowers the H^+** concentration in the CSF to maintain healthy pH in brain tissue.

Summary of Central Chemoreceptors

If these central chemoreceptors are triggered by elevated H^+, **this is an indication of elevated CO_2**, and the central chemoreceptors signal the **inspiratory centers**, such as the **DRG** to initiate contraction of the diaphragm and external intercostal muscles. As a result, the rate and depth of respiration increases, allowing more CO_2 to be expelled, and also bringing more air into the lungs promoting a reduction in the blood levels of CO_2.

In contrast, **low levels of CO_2 in the blood** cause low levels of H^+ in the CSF of brain, leading to **a decrease in the rate and depth of pulmonary ventilation**, producing shallow, slow breathing. In fact, if CO_2 levels become too low, the incoming signals will **stop ventilation altogether**! This again underscores the sensitivity of the respiratory system to CO_2 levels. An example can be seen if someone is blowing up balloons or an air mattress too quickly, they may become faint, not due to lack of breathing at first, but due to blowing off too much CO_2 that triggers the body to stop breathing. The same effect will occur during

hyperventilation, as this is 'over' breathing beyond metabolic need and can cause the CO_2 levels to become too low. This is why if someone becomes anxious and starts to hyperventilate, the suggestion of breathing into a **paper bag** is sound. The air exhaled into the paper bag contains high CO_2 levels and breathing it back into the lungs will help maintain sufficient CO_2 levels to sustain breathing.

Oxygen Sensitivity

Of the three chemicals that stimulate the chemoreceptors, it is the **O_2** levels of the blood that are the least impactful on these chemoreceptors compared to CO_2 and H^+ levels. The blood levels of O_2 are still very important in influencing respiratory rate, but the changes in O_2 levels must be much larger in order to stimulate the peripheral chemoreceptors. Another way of putting it is that the peripheral chemoreceptors are the least sensitive to changes in O_2.

We know that the PO_2 of arterial blood in the systemic circuit is **100 mmHg**, as that blood has come from the lungs and is going to the body to drop off O_2. If blood O_2 levels become very low, about **60 mmHg** or less in arterial blood, then peripheral chemoreceptors will be stimulated and trigger an increase in respiratory activity. This is a **40%** drop from normal blood O_2 levels. If there is a drop in arterial PO_2 to 80 mmHg the peripheral chemoreceptors will not be triggered.

Peripheral chemoreceptors only detect dissolved O_2 molecules, and not O_2 that is bound to Hb. Remember that the vast majority (98%) of O_2 is bound to Hb. When the dissolved levels of O_2 drop, the Hb releases O_2 and this results in these chemoreceptors requiring a large drop in O_2 levels in order to detect these changes in the of the aortic arch and the carotid arteries.

Summary of Other Regions of the Brain can Influence Respiration

The **cerebrum**, the **limbic system** and the **hypothalamus** can play a role in influencing the regulation of breathing by interacting with the respiratory centers in the medulla oblongata and the pons. Higher brain centers involved in conscious thought can alter breathing.

A simple example is if you decide to **hold your breath**. There is a limit to how long a person can do this, when needed, the respiratory control centers will take over once they determined the need to re-establish homeostasis. **Speaking** and **singing** also involve deliberate control of breathing patterns. In addition, the hypothalamus and other regions associated with the limbic system are involved in regulating respiration in response to **emotions**, **pain**, and **body temperature**, as these can impact breathing.

For example, feeling nervous, excited or scared (the fight-or-flight response) will result in an increase in respiratory rate. The sensation of pain can also illicit rapid breathing. Also, an increase in body temperature causes an increase in respiratory rate in an attempt to cool off.

The **central chemoreceptors** are specialized receptors situated in the brain and brainstem. Changes in the concentration of specific substances within the cerebrospinal fluid (CSF) bathing these regions, such as carbon dioxide or hydrogen ions, will stimulate these receptors which then signal the respiration centers of the brain that have been discussed above.

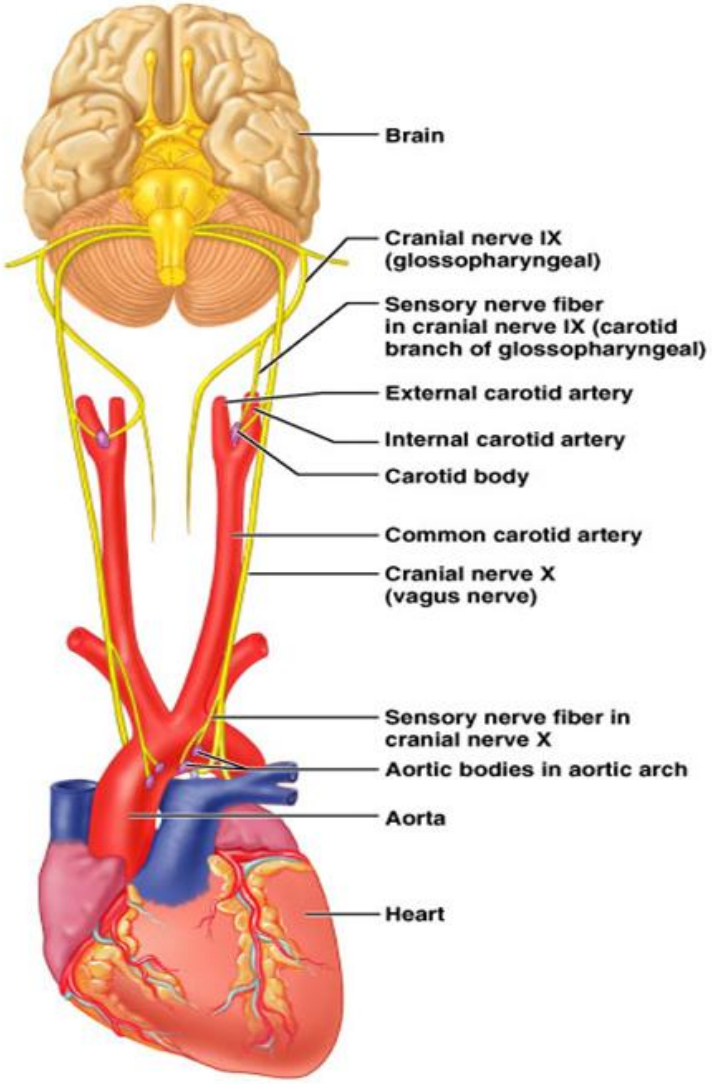

Figure 19.6 This drawing shows the key nerves that detect changes in blood chemistry at the aortic arch (delivering blood to the body) and at the carotid sinus arch (delivering blood to the brain).

Review Questions for Chapter 19: Respiratory Control

1. The region in the brain that sets the normal rhythmic pace of breathing is the _____.
- **a)** pons
- **b)** apneustic center
- **c)** arterial blood chemistry
- **d)** medulla oblongata
- **e)** a and d

2. The most important regulator of respiration in the body is
- **a)** O_2
- **b)** CO_2
- **c)** CO
- **d)** H^+
- **e)** HCO_3^-

3. Where in the body are the peripheral chemoreceptors located?
- **a)** the neck and legs
- **b)** the medulla oblongata
- **c)** carotid and aortic arteries
- **d)** pons
- **e)** all of these

4. Which of the following areas of the brain can influence a person's breathing? Select all that apply.
1. pons
2. limbic system
3. medulla oblongata
4. cerebellum
5. thalamus
6. cerebrum

5. Mechanoreceptors in the respiratory system are used for what purpose? To
- **a)** stimulate ventilation
- **b)** detect and prevent over inflation of the lungs
- **c)** prevent hyperventilation
- **d)** signal the pons to set rhythmic pace
- **e)** detect changes in blood chemistry & prevent over inflation

6. If breathing air at 30m under water, which effects are likely on the body from changes in pressure? Select all that apply.
1. Oxygen narcosis
2. Decreased solubility of N_2
3. Increased reactivity of H_2
4. Decreased solubility of CO_2
5. Increased solubility of O_2
6. Nitrogen narcosis

7. What does the **pneumotaxic** center do?

a) for strong, deep, sustained inspiratory movements
b) prevents the over inflation of lungs
c) decreased ventilation rate
d) inhibits the apneustic center
e) b and d

8. What does the ventral respiratory group within the medulla oblongata do?

a) triggers inspiration
b) decreased ventilation rate
c) nothing
d) for forced breathing
e) inhibits apneustic center, sets limits to over inflation of lungs

9. Where in the brain is the center responsible for 'overdrive' during inspiration located?

a) hypothalamus
b) cerebellum
c) pons
d) medulla oblongata
e) cerebrum

10. If you were hyperventilating, why would breathing into a paper bag prevent you from fainting?

a) it increases P_{CO2} of blood, signaling you to continue breathing
b) it increases the affinity of CO_2 for Hb
c) it increases P_{O2} of blood, signals you to stop breathing
d) it decreases P_{CO2} of blood, signals you to continue breathing

Answers in Appendix B