Regulation of respiration

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Control of breathing

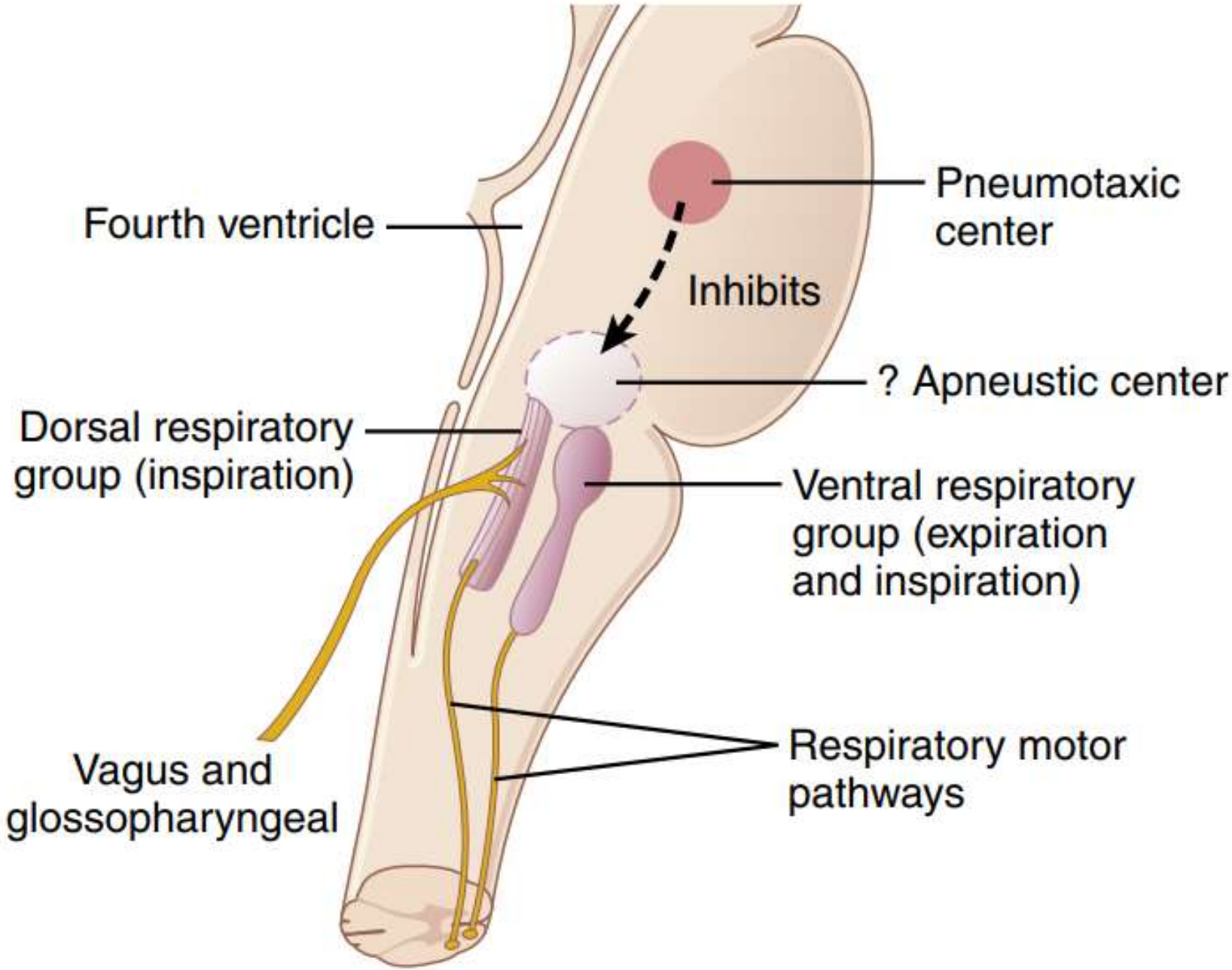
- The volume of air inspired and expired per unit time is tightly controlled, both with respect to frequency of breaths and to tidal volume.

- Breathing is regulated so that the lungs can maintain the PaO_2 and $PaCO_2$ within the normal range, even under widely varying conditions such as exercise

Respiratory center

- The respiratory center is composed of several groups of neurons located bilaterally in the medulla oblongata and pons of the brain stem.
- It is divided into three major collections of neurons:

- (1) a dorsal respiratory group, located in the dorsal portion of the medulla, which mainly causes inspiration.
- (2) a ventral respiratory group, located in the ventrolateral part of the medulla, which mainly causes expiration.
- (3) the pneumotaxic center, located dorsally in the superior portion of the pons, which mainly controls rate and depth of breathing.

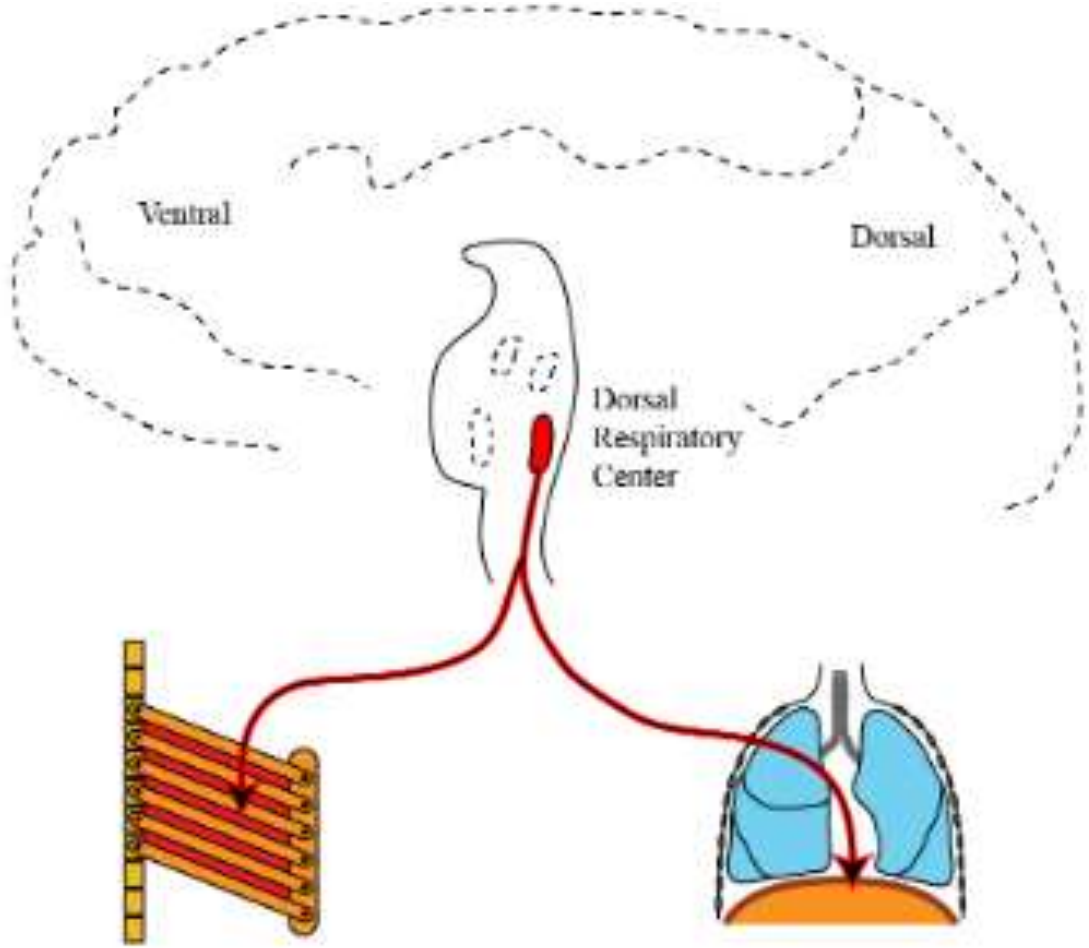

Fourth ventricle
Pneumotaxic center
Inhibits
? Apneustic center
Dorsal respiratory group (inspiration)
Ventral respiratory group (expiration and inspiration)
Vagus and glossopharyngeal
Respiratory motor pathways

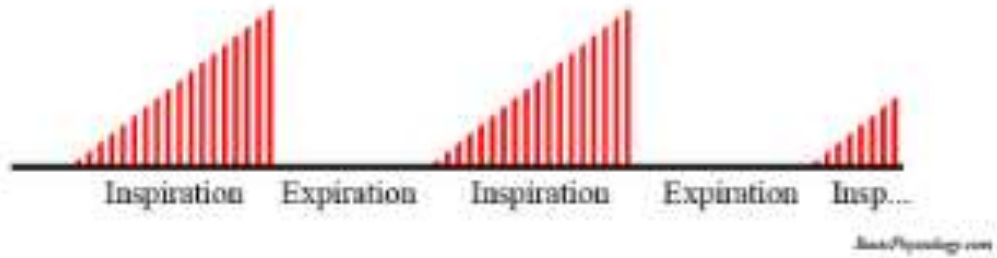
Inspiratory center (DRG)

- The nervous signal that is transmitted to the inspiratory muscles, mainly the diaphragm, is not an instantaneous burst of action potentials.

- Instead, it begins weakly and increases steadily in a ramp manner for about 2 seconds in normal respiration.

- It then ceases abruptly for approximately the next 3 seconds, which turns off the excitation of the diaphragm and allows elastic recoil of the lungs and chest wall to cause expiration.


Ventral
Dorsal
Dorsal
Respiratory
Center


Inspiration
Expiration
Inspiration
Expiration
Insp...

Inspiratory center (DRG)

- Next, the inspiratory signal begins again for another cycle; this cycle repeats again and again, with expiration occurring in between.

- Thus, **the inspiratory signal is a ramp signal**.

- The obvious advantage of the ramp is that it causes a steady increase in the volume of the lungs during inspiration, rather than inspiratory gasps.

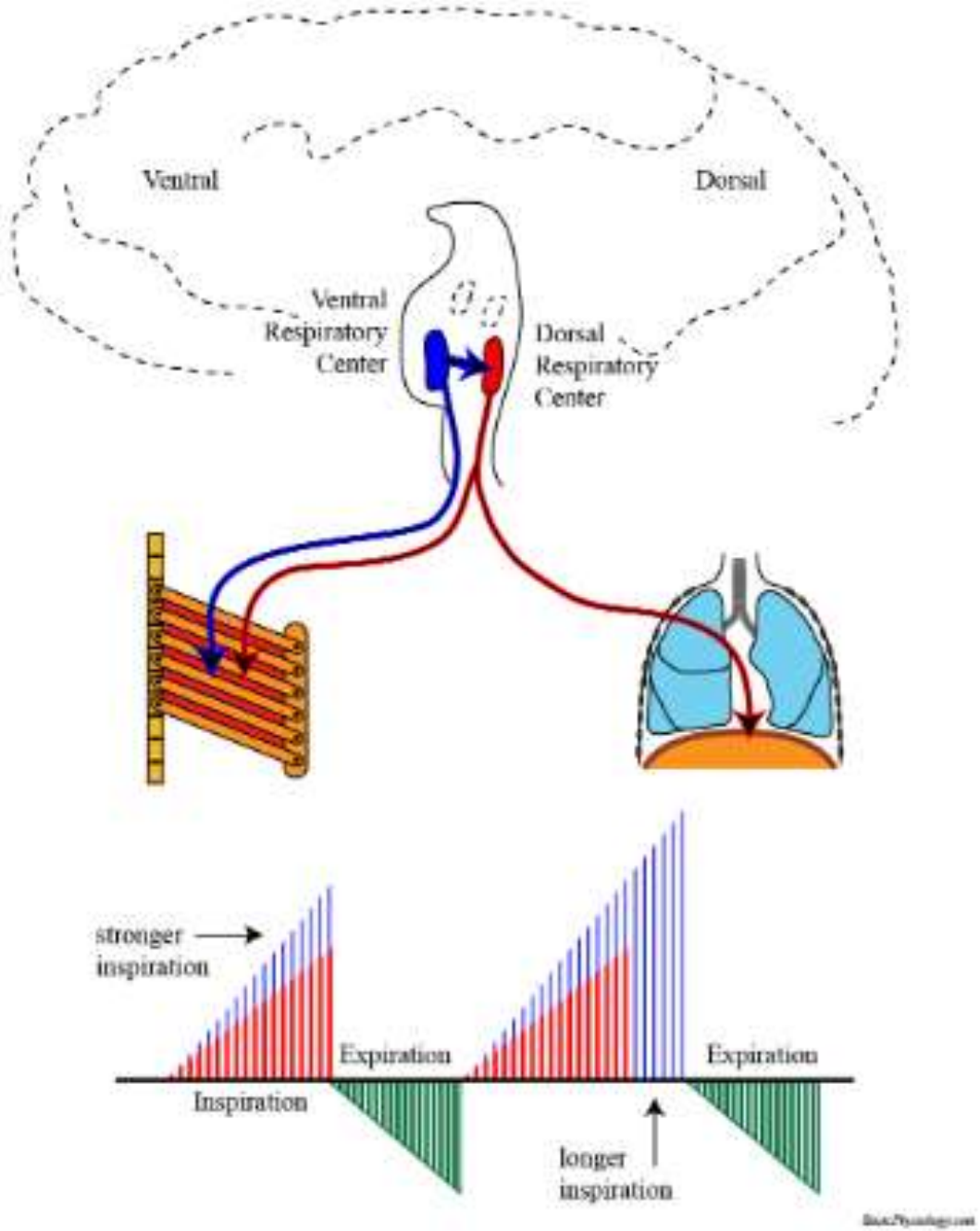
Inspiratory center (DRG)

- Two qualities of the inspiratory ramp are controlled, as follows:

- 1. Control of the rate of increase of the ramp signal so that during heavy respiration, the ramp increases rapidly and therefore fills the lungs rapidly.

- 2. Control of the limiting point at which the ramp suddenly ceases, which is the usual method for controlling the rate of respiration.

- That is, the earlier the ramp ceases, the shorter the duration of inspiration. This method also shortens the duration of expiration. Thus, the frequency of respiration is increased.


Ventral
Dorsal
Ventral
Respiratory
Center
Dorsal
Respiratory
Center
stronger
inspiration
Expiration
Expiration
Inspiration
longer
inspiration

Inspiratory center (DRG)

- The dorsal respiratory group (DRG) of neurons controls the basic rhythm for breathing by setting the frequency of inspiration.
- This group of neurons receives sensory input from peripheral chemoreceptors via the glossopharyngeal (CN IX) and vagus (CN X) nerves and from mechanoreceptors in the lung via the vagus nerve.
- The inspiratory center sends its motor output to the diaphragm via the phrenic nerve.
- Inspiration can be shortened by inhibition of the inspiratory center via the pneumotaxic center.

Pneumotaxic center

- The primary effect of this center is to control the “switch-off” point of the inspiratory ramp, thereby controlling the duration of the filling phase of the lung cycle.

- When the pneumotaxic signal is strong, inspiration might last for as little as 0.5 second, thus filling the lungs only slightly; when the pneumotaxic signal is weak, inspiration might continue for 5 or more seconds, thus filling the lungs with much greater amounts of air.

Expiratory center (VRG)

- The neurons of the ventral respiratory group remain almost totally inactive during normal quiet respiration.

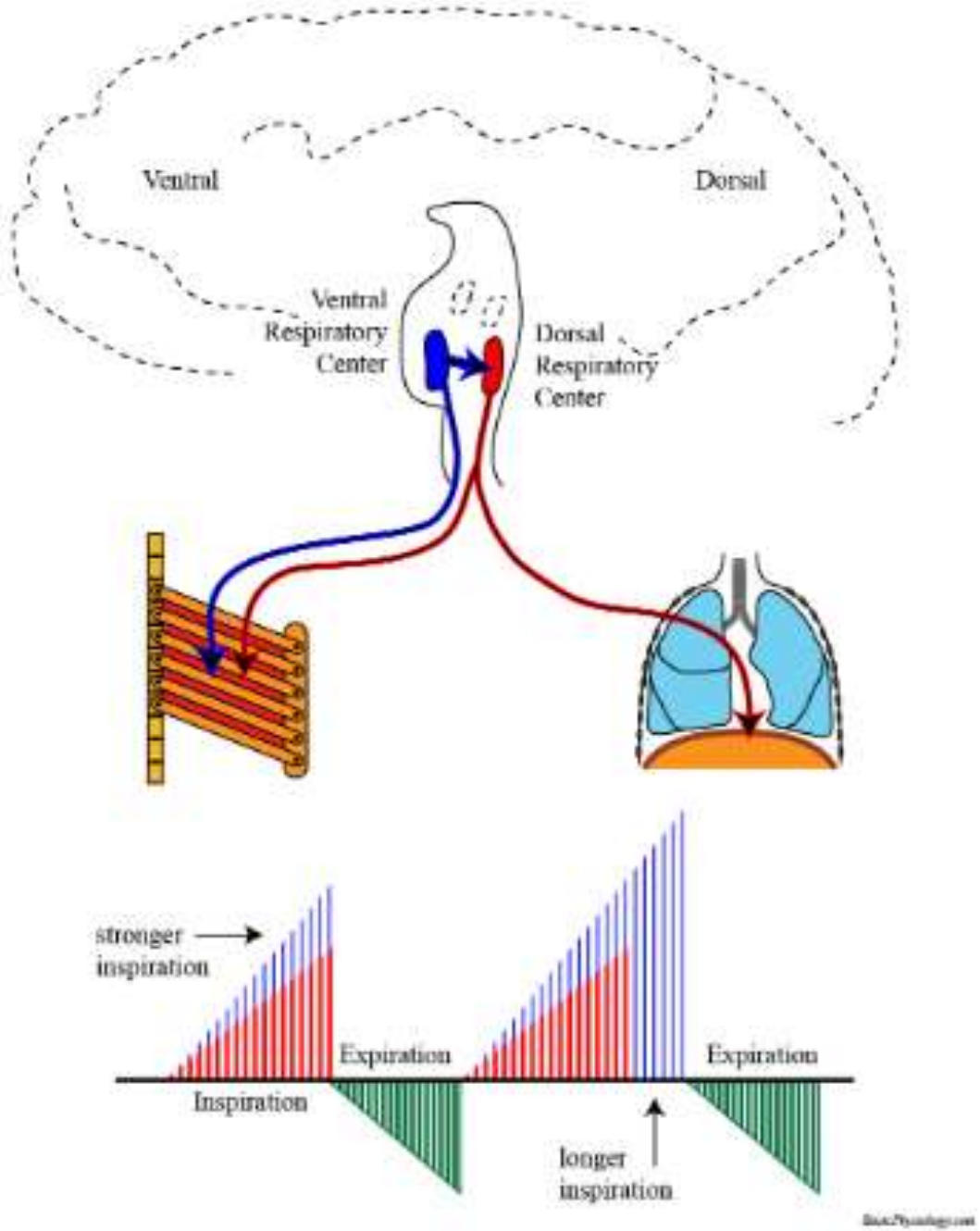
- Therefore, normal quiet breathing is caused only by repetitive inspiratory signals from the dorsal respiratory group transmitted mainly to the diaphragm, and expiration results from elastic recoil of the lungs and thoracic cage.

Expiratory center (VRG)

- Electrical stimulation of a few of the neurons in the ventral group causes inspiration, whereas stimulation of others causes expiration. Therefore, these neurons contribute to both inspiration and expiration.

- They are especially important in providing the powerful expiratory signals to the abdominal muscles during very heavy expiration.

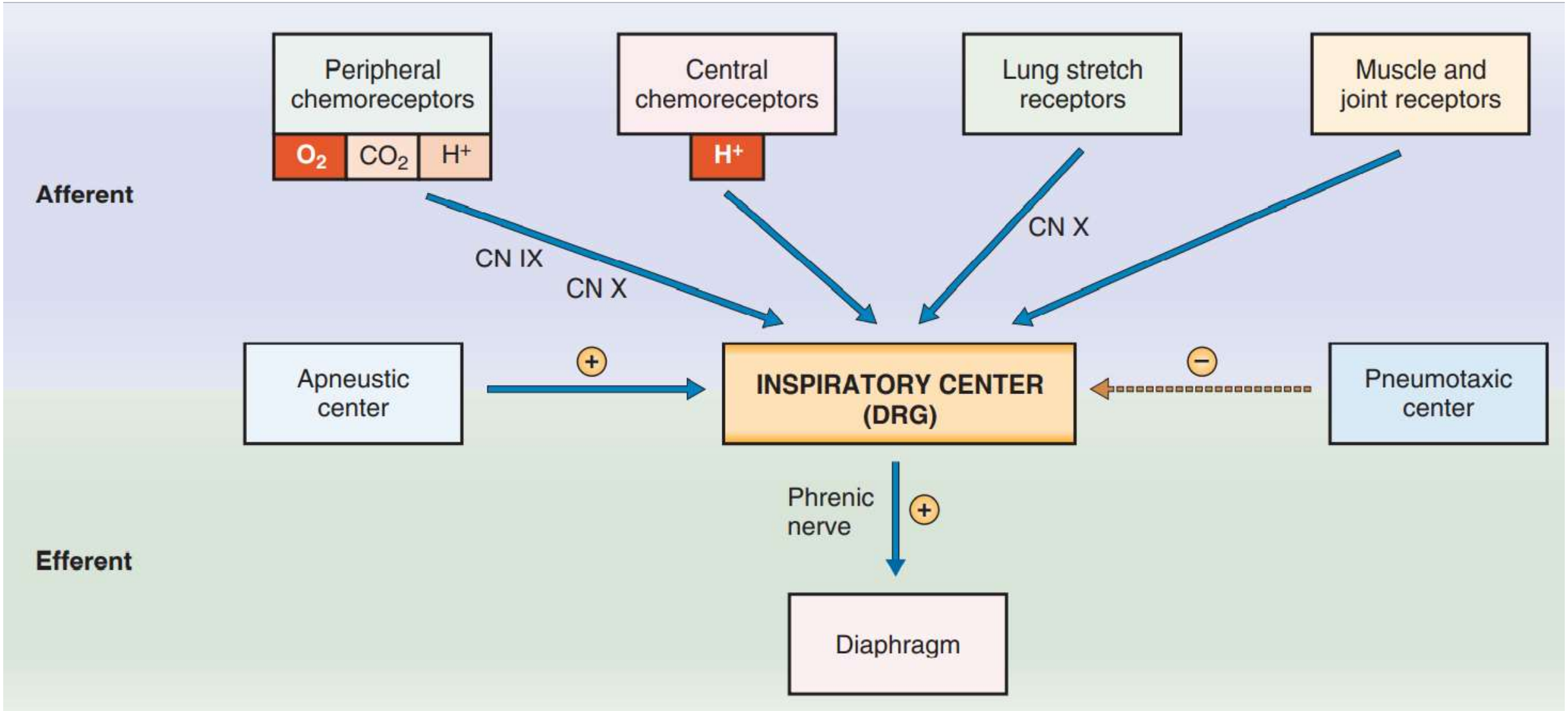
- Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required, especially during heavy exercise.


Ventral
Dorsal
Ventral
Respiratory
Center
Dorsal
Respiratory
Center
stronger
inspiration
Expiration
Expiration
Inspiration
longer
inspiration

Apneustic center

- Apneusis is an abnormal breathing pattern with prolonged inspiratory gasps, followed by brief expiratory movement.

- Stimulation of these neurons apparently excites the inspiratory center in the medulla, prolonging the period of action potentials in the phrenic nerve, and thereby prolonging the contraction of the diaphragm.


Peripheral chemoreceptors
O_2
CO_2
H^+
Central chemoreceptors
H^+
Lung stretch receptors
Muscle and joint receptors
Afferent
CN IX
CN X
CN X
Apneustic center
+
INSPIRATORY CENTER (DRG)
−
Pneumotaxic center
Phrenic nerve
+
Efferent
Diaphragm

Lung stretch receptors

- located in the muscular portions of the walls of the bronchi and bronchioles throughout the lungs are stretch receptors that transmit signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched.

- These stretch receptors activate an appropriate feedback response that "switches off" the inspiratory ramp and thus stops further inspiration.

- This mechanism is called the **Hering-Breuer inflation reflex**.

Lung stretch receptors

- This reflex also increases the rate of respiration, as is true for signals from the pneumotaxic center.

- In humans, the Hering-Breuer reflex probably is not activated until the tidal volume increases to more than three times normal (>≈1.5 L/breath).

- Therefore, this reflex appears to be mainly a protective mechanism for preventing excess lung inflation rather than an important factor in normal control of ventilation.

Cerebral cortex

- Commands from the cerebral cortex can temporarily override the automatic brain stem centers.

- For example, a person can voluntarily hyperventilate (i.e., increase breathing frequency and volume).

- The consequence of hyperventilation is a decrease in $PaCO_2$, which causes arterial pH to increase.

Cerebral cortex

- Hyperventilation is self-limiting, because the decrease in $PaCO_2$ will produce unconsciousness and the person will revert to a normal breathing pattern.

- Although more difficult, a person may voluntarily hypoventilate (i.e., breath-holding).

- Hypoventilation causes a decrease in PaO_2 and an increase in $PaCO_2$, both of which are strong drives for ventilation. A period of prior hyperventilation can prolong the duration of breath-holding.

Chemical control of respiration

- The ultimate goal of respiration is to maintain proper concentrations of O_2, CO_2, and H^+ in the tissues.

- The respiratory activity is highly responsive to changes in each of these substances.

- Excess CO_2 or excess H^+ in the blood mainly act directly on the respiratory center, causing greatly increased strength of both the inspiratory and the expiratory motor signals to the respiratory muscles.

Chemical control of respiration

- O2, in contrast, does not have a major direct effect on the respiratory center of the brain in controlling respiration.

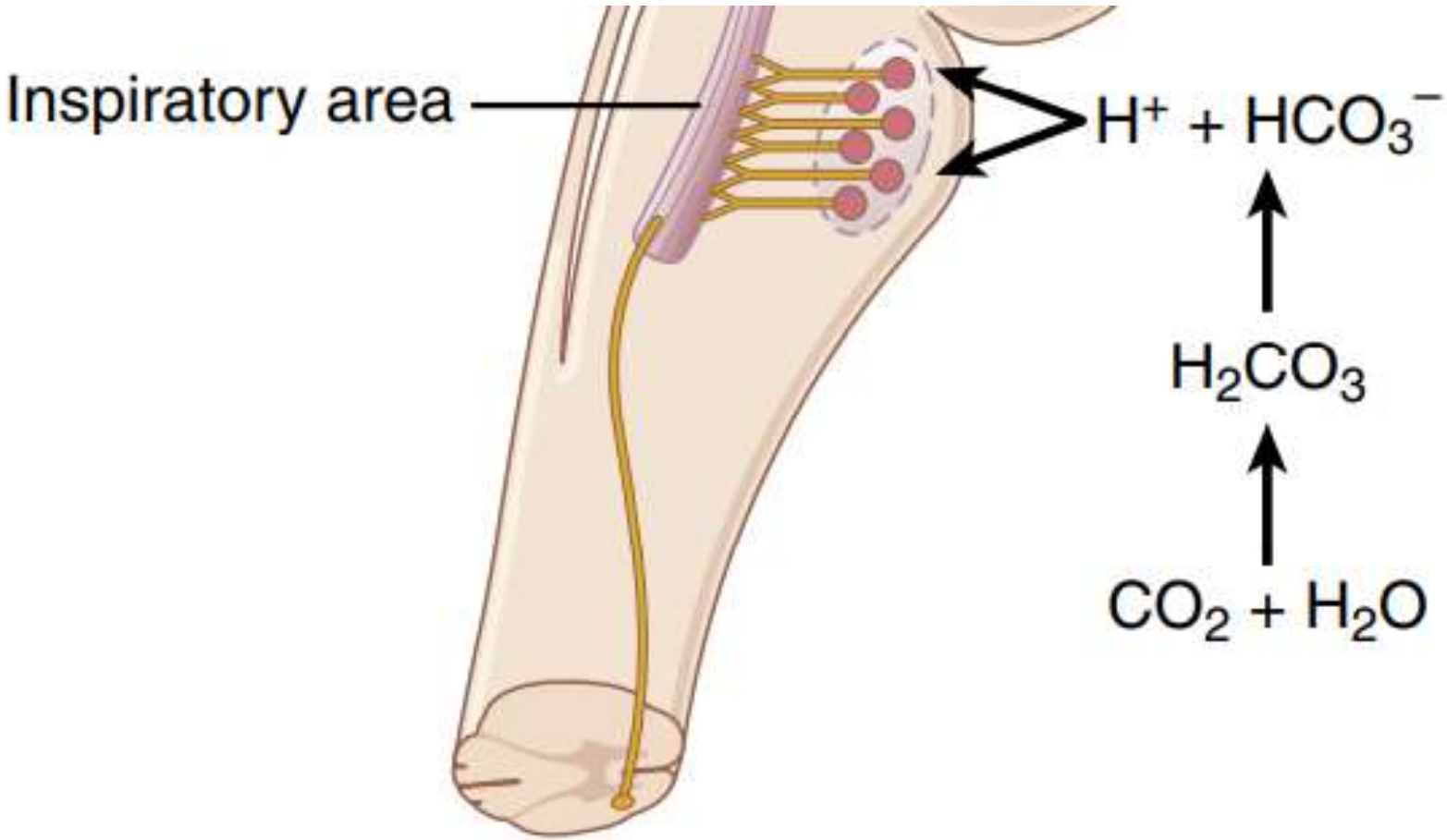
- Instead, it acts almost entirely on peripheral chemoreceptors located in the carotid and aortic bodies, and these chemoreceptors in turn transmit appropriate nervous signals to the respiratory center for control of respiration.

Central chemoreceptors

- The sensor neurons in the chemosensitive area are especially excited by H+; in fact, it is believed that H+ may be the only important direct stimulus for these neurons.

- However, H+ ions do not easily cross the blood–brain barrier.

- For this reason, changes in H+ concentration in the blood have considerably less effect in stimulating the chemosensitive neurons than changes in blood CO2, even though CO2 is believed to stimulate these neurons secondarily by changing the H+ concentration,


Inspiratory area
$H^+ + HCO_3^-$
H_2CO_3
$CO_2 + H_2O$

Central chemoreceptors

- Although CO2 has little direct effect in stimulating the neurons in the chemosensitive area, it does have a potent indirect effect.

- It has this effect by reacting with the water of the tissues to form carbonic acid, which dissociates into H+ and HCO3−; the H+ then have a potent direct stimulatory effect on respiration.

Central chemoreceptors

- Excitation of the respiratory center by CO_2 is great the first few hours after the blood CO_2 first increases, but then it gradually declines over the next 1 to 2 days.

- Part of this decline results from renal readjustment of the H^+ concentration in the circulating blood back toward normal after the CO_2 first increases the H^+ concentration.

- The kidneys achieve this readjustment by increasing the blood HCO_3^-, which binds with H^+ in the blood and cerebrospinal fluid to reduce their concentrations.

Central chemoreceptors

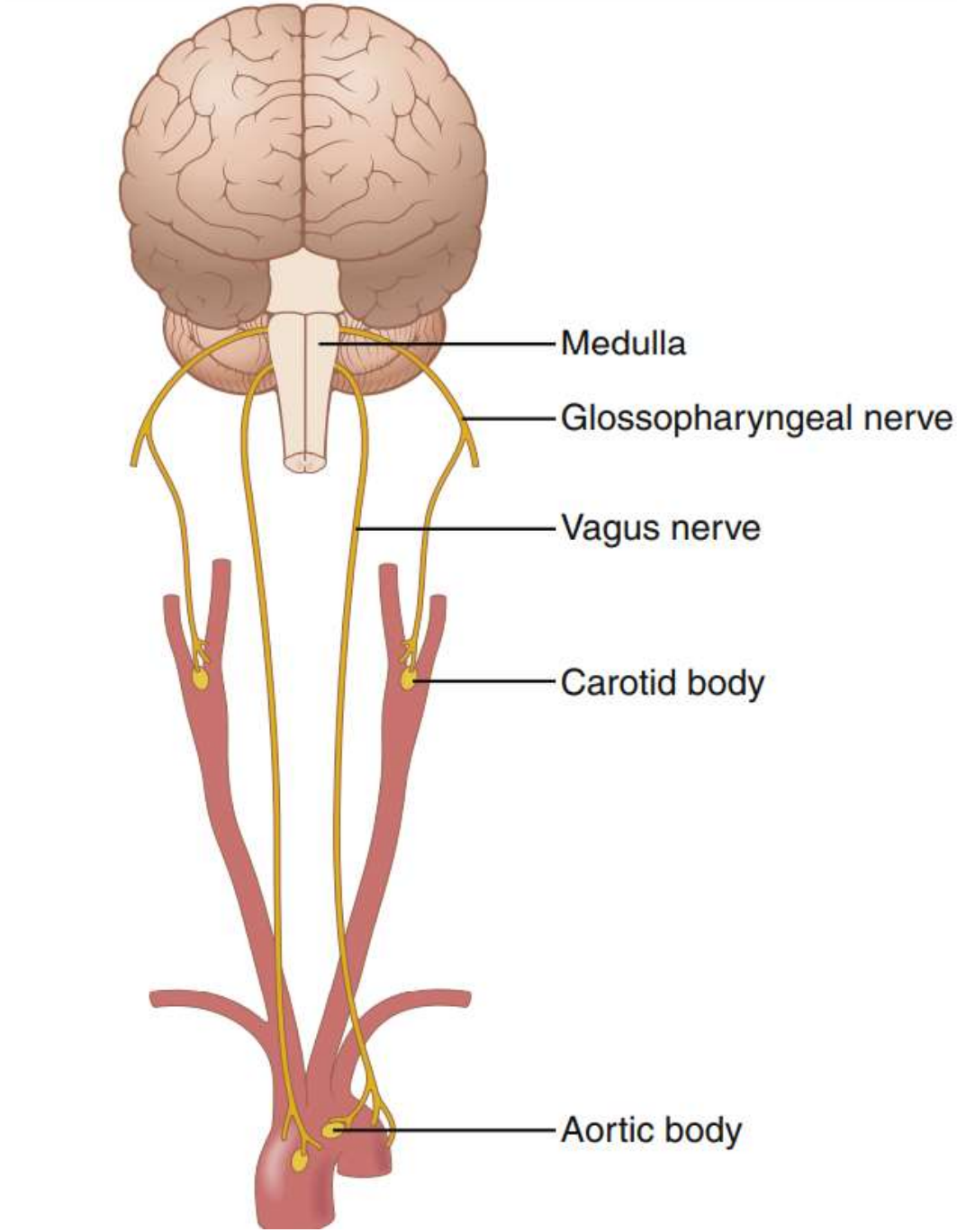
- But, even more importantly, over a period of hours, the HCO_3^- also slowly diffuses through the blood–brain and blood–cerebrospinal fluid barriers and combine directly with H^+ adjacent to the respiratory neurons as well, thus reducing the H^+ back to near normal.

- A **change in blood CO_2** concentration therefore has a **potent acute effect** on controlling respiratory drive but only a **weak chronic effect** after a few days' adaptation

Peripheral chemoreceptors

- There are peripheral chemoreceptors for O_2, CO_2, and H^+ in the carotid bodies located at the bifurcation of the common carotid arteries and in the aortic bodies.

- Information about arterial PO_2, PCO_2, and pH is relayed to the DRG via CN IX and CN X, which orchestrates an appropriate change in breathing rate.


Medulla
Glossopharyngeal nerve
Vagus nerve
Carotid body
Aortic body

Peripheral chemoreceptors

- They are especially important for **detecting changes in O2** in the blood, although they also respond to a lesser extent to changes in CO2 and H+ concentrations.

- The chemoreceptors transmit nervous signals to the respiratory center in the brain to help regulate respiratory activity.

- Most of the chemoreceptors are in the carotid bodies. However, a few are also in the aortic bodies, and a very few are located elsewhere in association with other arteries.

Peripheral chemoreceptors

- Each of the chemoreceptor bodies receives its own special blood supply through a minute artery directly from the adjacent arterial trunk.

- Blood flow through these bodies is extreme, 20 times the weight of the bodies themselves each minute.

- Therefore, the percentage of O2 removed from the flowing blood is virtually zero, which means that the chemoreceptors are exposed at all times to arterial blood, not venous blood, and their Po2 values are arterial Po2 values.

Peripheral chemoreceptors

- When the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated.

- The impulse rate is particularly sensitive to changes in arterial Po2 in the range of 60 mm Hg down to 30 mm Hg, a range in which hemoglobin saturation with oxygen decreases rapidly.

Peripheral chemoreceptors

- An increase in CO2 or H+ concentration also excites the chemoreceptors and, in this way, indirectly increases respiratory activity.

- However, the direct effects of both these factors in the respiratory center are much more powerful than their effects mediated through the chemoreceptors (about seven times as powerful).

Peripheral chemoreceptors

- There is one difference between the peripheral and central effects of CO2—the stimulation via the peripheral chemoreceptors occurs as much as five times as **rapidly** as central stimulation, so the peripheral chemoreceptors might be especially important in increasing the rapidity of response to CO2 at the onset of exercise.

Peripheral chemoreceptors

- Mountain climbers have found that when they ascend a mountain slowly, over a period of days rather than a period of hours, they breathe much more deeply and therefore can withstand far lower atmospheric O2 concentrations than when they ascend rapidly.

- This phenomenon is called **acclimatization**.

- The reason for acclimatization is that within 2 to 3 days, the respiratory center in the brain stem loses about 80% of its sensitivity to changes in Pco2 and H+.

Peripheral chemoreceptors

- Therefore, the excess ventilatory blow-off of CO2 that normally would inhibit an increase in respiration fails to occur, and low O2 can drive the respiratory system to a much higher level of alveolar ventilation than under acute conditions.

- Instead of the 70% increase in ventilation that might occur after acute exposure to low O2, the alveolar ventilation often increases by 400% to 500% after 2 to 3 days of low O2, which helps immensely in supplying additional O2 to the mountain climber

aPO2

- Decreases in arterial PO2.
- The most important responsibility of the **peripheral chemoreceptors** is to detect changes in arterial PO2.
- They respond dramatically when PO2 decreases to less than 60 mm Hg.
- Thus if arterial PO2 is between 100 mm Hg and 60 mm Hg, the breathing rate is virtually constant. However, if arterial PO2 is less than 60 mm Hg, the breathing rate increases in a steep and linear fashion.

aPCO2

- The peripheral chemoreceptors also detect increases in PCO2, but the effect is less important than their response to decreases in PO2.

- Detection of changes in PCO2 by the peripheral chemoreceptors also is less important than detection of changes in PCO2 by the **central chemoreceptors.**

pH

- Decreases in arterial pH cause an increase in ventilation, mediated by peripheral chemoreceptors for H+.

- This effect is independent of changes in the arterial PCO2 and is mediated only by chemoreceptors in the carotid bodies (not by those in the aortic bodies).

- Thus in metabolic acidosis, in which there is decreased arterial pH, the peripheral chemoreceptors are stimulated directly to increase the ventilation rate

Joint and muscle receptors

- Mechanoreceptors located in the joints and muscles detect the movement of limbs and instruct the inspiratory center to increase the breathing rate.

- Information from the joints and muscles is important in the early (anticipatory) ventilatory response to exercise.

Irritant receptors

- Irritant receptors for noxious chemicals and particles are located between epithelial cells lining the airways.

- Information from these receptors travels to the medulla via CN X and causes a reflex constriction of bronchial smooth muscle and an increase in breathing rate.

J receptors

- Juxtacapillary (J) receptors are located in the alveolar walls and therefore are near the capillaries.

- Engorgement of pulmonary capillaries with blood and increases in interstitial fluid volume may activate these receptors and produce an increase in the breathing rate.

- For example, in left-sided heart failure, blood “backs up” in the pulmonary circulation and J receptors mediate a change in breathing pattern, including rapid shallow breathing and dyspnea (difficulty in breathing).

Thank you