Control of Ventilation
(Regulation of Respiration)

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Lecture objectives:

1. Describe the general organization of the respiratory control system.
2. Identify the regions in the central nervous system that play important roles in the generation and control of cyclic breathing.
3. Describe the central and peripheral chemoreceptors and their role in the control of ventilation.
4. List the anatomical locations of chemoreceptors sensitive to changes in arterial PO_2, PCO_2, and pH that participate in the control of ventilation.
5. Describe the effects of alterations in body oxygen, carbon dioxide, and hydrogen ion levels on the control of breathing and understand the integrated responses to CO_2, hypoxia, pH and identify the relative importance of each in sensing alterations in blood gasses.
6. List the cardiopulmonary and other reflexes that influence the breathing pattern.
7. State the ability of the brain cortex to override the normal pattern of inspiration and expiration temporarily.
8. Discuss the regulation of ventilation in chronic respiratory failure.

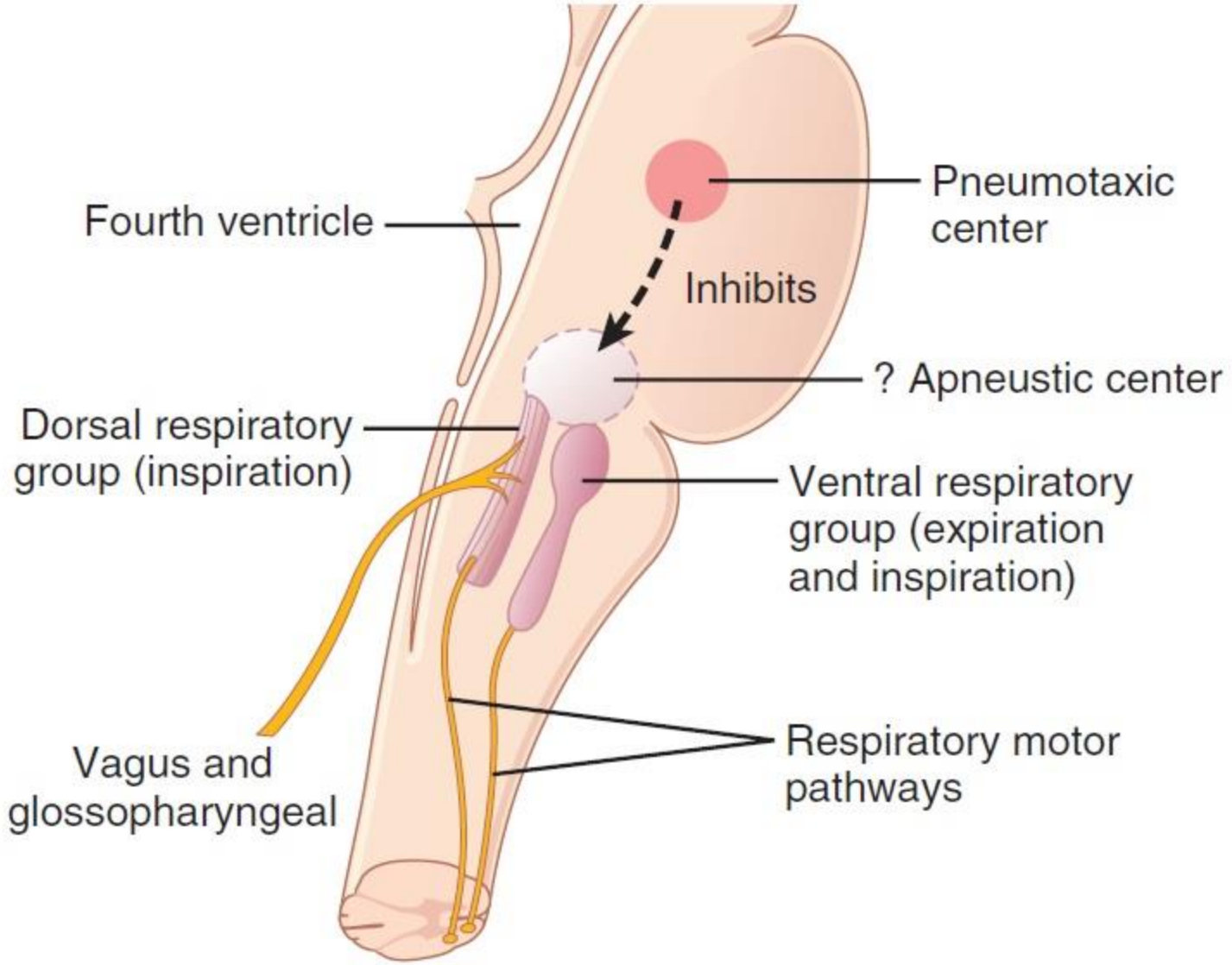
The Respiratory Center

Function: The respiratory center adjusts alveolar ventilation to meet the demands so PO_2 and PCO_2 in the arterial blood are held constant even during exercise.

Physiological anatomy: The respiratory center is composed of groups of neurons located bilaterally in the medulla oblongata and pons. These groups are;

- Dorsal respiratory group (DRG) (causes inspiration)
- Ventral respiratory group (VRG) (mainly causes expiration)
- Pneumotaxic center (controls the rate and depth of breathing). Located dorsally in the superior portion of the pons
- Apneustic center

Note: The pons, hypothalamus, reticular activating system (RAS), and the cerebral cortex as well as afferents from the vagus, glossopharyngeal, and somatic nerves influence both the DRG and VRG.



Organization of the respiratory center

Dorsal respiratory group (DRG):

- Neurons are almost located within the *nucleus of the tractus solitarius*. The neurons extends most of the length of the medulla.
- The nucleus of the tractus solitarius is the terminal station for the sensory part of the vagus and glossopharyngeal nerves (from chemoreceptors, baroreceptors, and other receptors in the lung).
- The DRG is the **pacemaker** for the basic respiratory rhythm. The intrinsic inspiratory rhythm starts with a latent period of several seconds during which there is no neuronal activity.
- Then bursts of action potentials begin to appear and are transmitted to the primary **inspiratory muscles** (through the phrenic nerve to the diaphragm) in a "**Ramp or Crescendo**" manner → No gasps.
- The ramp has a rate and limit (span) that can be controlled. The greater the increase in the rate the greater is the filling of the lung. Whereas, the shorter the limit the shorter is the respiratory cycle → higher respiratory rate.

The Pneumotaxic Center:

- Located dorsally in the *nucleus parabrachialis* of the upper pons.
- It controls the "switch-off" point of the inspiratory ramp in DRG (i.e. inhibits inspiration) and thus:
  - Regulate inspiration volume (tidal volume)
  - Controls respiratory rate.
- The tidal volume is inversely related to the respiratory rate.
- Strong stimulation of the pneumotaxic center can shorten inspiration for as little as 0.5 second.
- The function of the pneumotaxic center is primarily to limit inspiration, leading to a shallower and more rapid respiratory pattern.

Note:

It is believed that the pneumotaxic center is responsible for the “fine-tuning” of respiratory rhythm because a normal rhythm can exist in the absence of this center.

Ventral respiratory group (VRG):

- Neurons are located in the *nucleus ambiguus* and *nucleus retroambiguus*.
- VRG remains almost totally inactive during normal quiet respiration. Therefore, The ventral respiratory neurons do not appear to participate in the basic rhythmical oscillation that controls respiration.
- VRG has no pacemaker activity, but activated by the dorsal respiratory group to act and assist the dorsal group when greater pulmonary ventilation is needed (e.g. exercise).
- VRG supplies expiratory signals to the abdominal muscles during very heavy expiration.

The apneustic center:

- Located in the lower part of the pons.
- In experimental animal it inhibits the switch-off of the inspiratory ramp signals → increase tidal volume and duration of inspiration (prolonged inspiratory gasps or apneuses interrupted by transient expiratory efforts).
- In experimental animal impulses from this center prolong the ramp action potentials.
- Its activity is inhibited by the pneumotaxic center and by vagal impulses.
- Its importance in human respiration is ?????

Vagal signals (Hering-Breuer Inflation Reflex or the inspiratory inhibitory reflex)

- Stimulation of bronchial and bronchiolar stretch receptors → afferent signals through the vagus nerve via large myelinated fibers → inhibition of the DRG (similar to the signals from the pneumotaxic center).
- This reflex operates when tidal volume exceeds 1.5 L (i.e. three times the normal value). It is a protective mechanism.

Reticular Activating System (RAS):

The RAS stimulates the respiratory centers to increase respiratory drive.

During sleep, when RAS activity diminishes, there is a decrease in alveolar ventilation that leads to a slight elevation of arterial CO_2 tension.

Physiological Control of Respiration

The intensity of the respiratory control signals is increased or decreased to match the ventilatory needs of the body in many physiological and pathological states. Exercise; hypoxia; and metabolic acidosis or alkalosis are examples of such conditions.

The control mechanisms can be divided into **two** groups. These are;

1. Chemical control of respiration
2. Non-chemical (Neural) control of respiration

The respiratory receptors (The chemoreceptors):

1. Central chemoreceptors: are chemosensitive neurons located bilaterally, and are lying 0.2 millimeter beneath the ventral surface of the medulla in the vicinity of the exit of the 9th and 10th nerves.

   These neurons are sensitive to changes in either **PCO_2 or H^+** concentration in the surrounding interstitial fluid → Stimulation of the respiratory center.

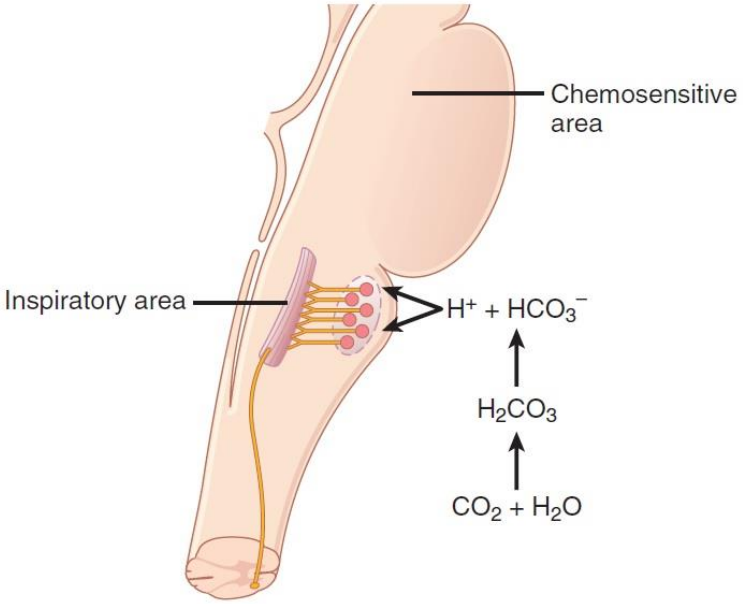
2. Peripheral chemoreceptors: are located in the **carotid** and **aortic bodies**. They mainly detect changes in **Oxygen** in the blood, and also respond to a lesser degree to changes in P_aCO_2 and H^+.

   Signals from the carotid and aortic bodies are transmitted through the glossopharyngeal nerve to the dorsal respiratory area of the medulla.

   The aortic bodies signals are sent through the vagi also to the dorsal respiratory area.

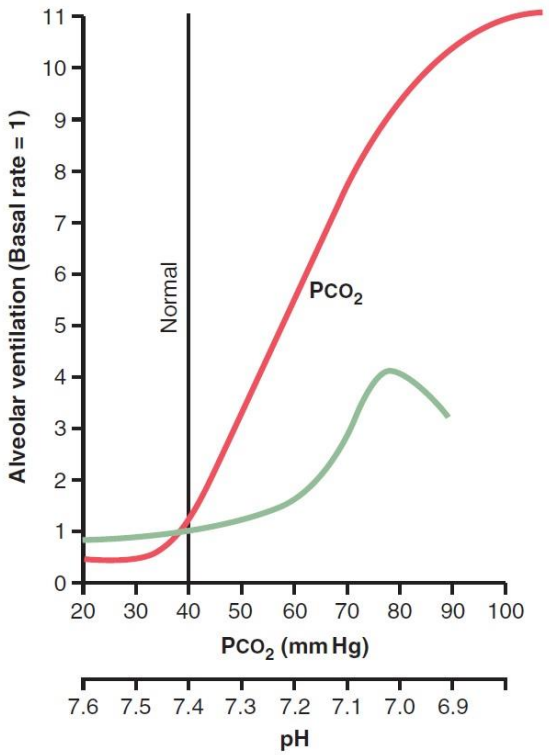
Chemical control:

1. Central chemoreceptors:
   - Hydrogen ions of the CSF are believed to be the only direct stimulus to the central receptors (i.e. the chemosensitive neurons). Changes in H^+ concentration in the blood have less stimulatory effect as H^+ does not easily cross the blood-brain barrier.
   - Changes in blood CO_2 can affect these receptors indirectly as blood-brain barrier is completely permeable to CO_2. Carbon dioxide reacts with H_2O in the CSF $\rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$. The H^+ then stimulates the central chemoreceptors.



Chemical control (cont.):

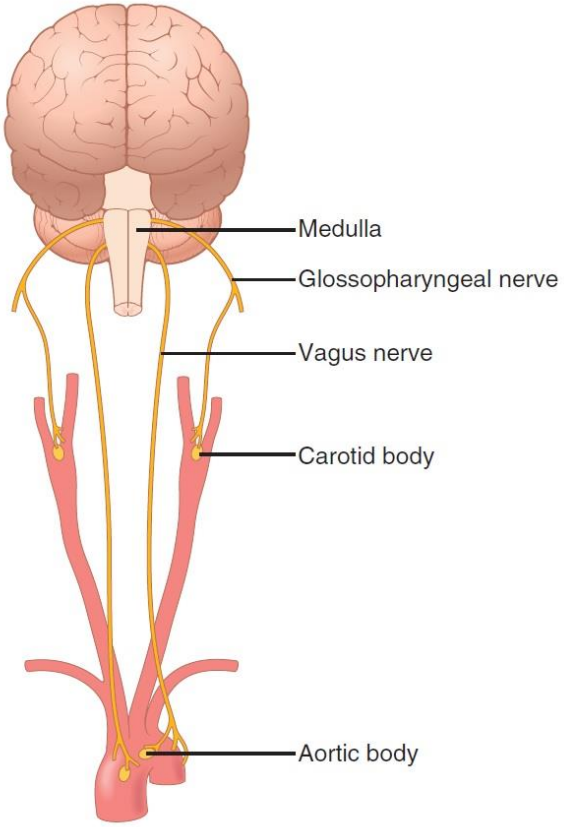
- Any increase in PCO_2 → ↑ strength of both the inspiratory and expiratory motor signals to the respiratory muscles.
- The initial **acute** increase in the respiratory drive when PCO_2 increases declines over the next 1-2 days because of the renal readjustment of the H^+ concentration (pH of the brain extracellular fluid returns to near normal in spite of a raised PCO_2). And only a weak **chronic** effect remains after a few days' adaptation.
- Approximately 85% of the resting, chemical drive of respiration results from the stimulatory effect of CO_2 on central chemoreceptors.
- Oxygen changes have no direct effect on central chemoreceptors. Therefore, CO_2 is the major controller of respiration, not oxygen.



Effects of increased arterial blood P_{CO_2} and decreased arterial pH (increased hydrogen ion concentration) on the rate of alveolar ventilation.

2. Peripheral chemoreceptors:

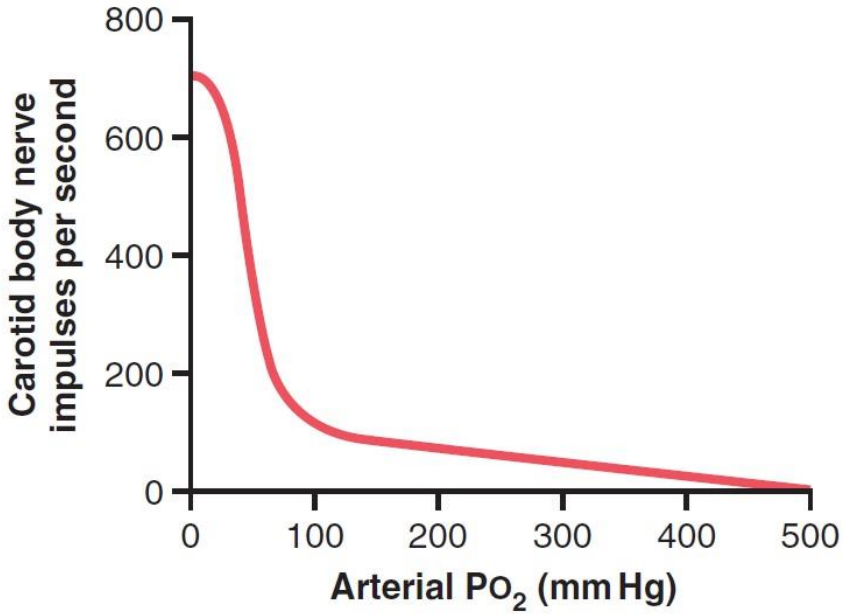
- They are the only site that detect changes in O_2 in the arterial blood, they respond to a lesser extent to changes in CO_2 and H^+.
- Decrease in PO_2 (below 70 mmHg) → stimulation of peripheral chemoreceptors → stimulation of DRG → increased rate and depth of respiration.
- An increase in either CO_2 or H^+ → stimulation of peripheral chemoreceptors → **Rapid** stimulation of respiration (as much as five times as rapidly as central stimulation).



Respiratory control by peripheral chemoreceptors in the carotid and aortic bodies.

2. Peripheral chemoreceptors:

- The increase in ventilatory drive due to arterial hypoxemia is multiplied if central chemoreceptors lose its sensitivity (because of adaptation). This is the basis of acclimatization to the low atmospheric oxygen concentration.
- (Acclimatization = deeper breathing 2-3 days after slow ascending of a mountain)



Note: The response of peripheral chemoreceptors is to the PO_2, not the oxygen concentration. Therefore, anemia and CO poisoning do not stimulate peripheral chemoreceptors.

Respiratory regulation during exercise:

- During exercise the increase in O_2 consumption and CO_2 formation can rise to as much as 20-fold. Yet in the healthy athlete, alveolar ventilation ordinarily increases almost exactly in step with the increased level of oxygen metabolism. The arterial PO_2, PCO_2, and pH remain almost exactly normal.
- The immediate increase in ventilation on the initiation of exercise, before blood chemical changes have time to develop, suggests that the respiratory changes are due to;
  1. Stimulatory impulses from higher centers of the brain to both the respiratory muscles and respiratory center.
  2. Proprioceptive stimulatory reflexes to the respiratory center.

Non-chemical factors that affect respiration:

1. Voluntary control of respiration: The cortex can override the function of the brainstem within limits. The nervous pathway passes directly from the cerebral cortex and other higher centers through the cortico-spinal tract.
2. Other parts of the brain, such as the limbic system and hypothalamus, can alter the pattern of breathing, for example, in emotional states such as **rage** and **fear**.
3. Coughing, sneezing, and even breath-holding (i.e. apnea): due to stimulation of **pulmonary irritant receptors**. These receptors are stimulated by noxious gases, cigarette smoke, inhaled dusts, and cold air. The response can also cause mucus secretion and bronchospasm as in asthma and emphysema.
4. The feeling of dyspnea when the pulmonary capillaries become engorged with blood (as in left heart failure) or when pulmonary edema occurs: is due to stimulation of **J receptors**, nonmyelinated sensory nerve endings positioned in the pulmonary interstitium that are in juxtaposition to the pulmonary capillaries. Their stimulation → tachypnea.
5. Anesthesia: can cause respiratory depression and respiratory arrest in overdosage.
6. Hering-Breuer reflex

Chronic respiratory failure:

- Chronic respiratory failure is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. It is classified as either hypoxemic or hypercapnic respiratory failure. The failure may be complicated by polycythemia or cor pulmonale.
- Hypoxemic respiratory failure is characterized by an arterial oxygen tension (PaO_2) lower than 60 mmHg with a normal or low arterial carbon dioxide tension ($PaCO_2$). This is the most common form of respiratory failure.
- Hypercapnic respiratory failure is characterized by a $PaCO_2$ higher than 50 mmHg. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. The patient suffers from respiratory acidosis.
- Respiratory acidosis occurs due to;

  1. Generalized hypoventilation and results from failure of the controller to respond to carbon dioxide (e.g., during anesthesia, following brain injury, and in some patients with chronic obstructive lung disease).
  2. Obstructive lung disease. When these patients breathe room air, hypercapnia caused by reduced alveolar ventilation is accompanied by significant hypoxia and acidosis.

Test Question:

Q. Concerning the respiratory centers?

A. The normal rhythmic pattern of breathing originates from neurons in the motor area of the cortex.
B. During quiet breathing, expiratory neurons fire actively.
C. Impulses from the pneumotaxic center can stimulate inspiratory activity.
D. The cortex of the brain can override the function of the respiratory centers.
E. The only output from the respiratory centers is via the phrenic nerves.