7. Regulation of breathing

Breathing is essentially automatic and can only be altered temporarily by voluntary efforts. You cannot consciously stop breathing for long. Breathing is finely tuned to meet metabolic demands, such that during exercise ventilation increases to maintain arterial PO_2, PCO_2 and pH within a narrow range. To achieve this tight regulation, peripheral receptors send information to a CNS respiratory center whose output adjusts initiation, duration, depth, and rate of breathing.

The intercostal muscles and diaphragm are skeletal muscles that will not contract unless stimulated. Thus breathing depends on cyclical excitation of the motor neurons that innervate these muscles. Destruction of these nerves by the polio virus for example results in paralysis and death if the individual is not ventilated.

The underlying respiratory rhythm is established by **respiratory centers** in the **medulla of the brain stem** (Fig 4). The general term for this integration center is the **respiratory rhythm generator**. Inspiratory neurons located in the respiratory center initiate respiratory rhythm by sending signals to the motor neurons that innervate the effector skeletal muscles (intercostals and diaphragm). This rhythm is modified by input from **peripheral sensors** (**chemoreceptors and mechanoreceptors)** located in blood vessel walls and by central receptors (chemoreceptors) in the brain.

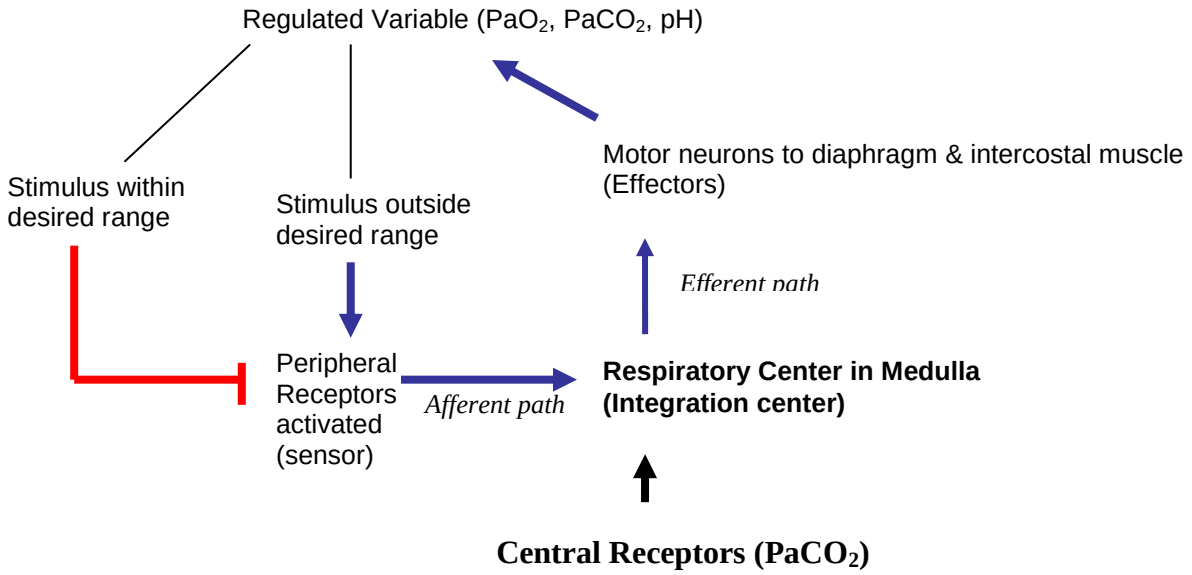

Figure 4. Reflex control of breathing.

Inspiration is limited by several inputs including stretch of the lungs and innate rhythm generators within the brain stem (medulla). The medullary inspiratory neurons are quite sensitive to drugs such as barbiturates and morphine. Death from an overdose of these drugs is often due to cessation of breathing.

Inspiratory receptors in the lung include:

1. Pulmonary stretch receptors located in the smooth muscle of the large and small airways of the lung are mechanoreceptors that fire with the inflation of the lung. These receptors **stop inspiration** as part of the **Hering-Breuer reflex**. In the adult this reflex is evoked only under conditions of large tidal volumes as in rigorous exercise.

2. J Receptors located in the walls of the pulmonary capillaries which are stimulated by pulmonary vascular congestion, edema, air emboli (air in the blood), and low lung volumes. Stimulation of these receptors can result in **rapid breathing** (**hyperpnea)**, and or labored breathing (**dyspnea).**

3. Pulmonary irritant receptors located in airway epithelium and the nasal mucosa. Mechanical or chemical irritation elicits a **cough reflex** and **bronchoconstriction**.

Transport of Hydrogen Ions

Metabolism generates protons (H+) which are extruded to the interstitial fluid surrounding cells and eventually enter the blood by diffusion. As blood flows through the tissues, a fraction of the oxy-hemoglobin (O_2-Hb) loses its oxygen to become deoxy-Hb. Deoxy-Hb has a much higher affinity for H+ and thus binds most of the newly generated H+.

$HbO_2 + H+ = HbH + O_2$

This effectively removes the H+ from the blood and thereby buffers the blood. As a consequence venous blood is slightly more acidic (pH of 7.36) than arterial blood (pH 7.4).

As venous blood passes through the lungs, HbH is converted to HbO_2 and H+ is released. The H+ reacts with the bicarbonate (HCO_3-) in the blood to give carbonic acid (H_2CO_3) which dissociates to $H_2O + CO_2$. The CO_2 diffuses into the alveoli to be expired. **Normally all of the H+ will be removed** by this process and none will appear in the arterial blood.

$H+ + HCO_3- = H_2CO_3 = H_2O + CO_2$

However, if an individual is either **hypoventilating** or has a lung disease that prevents normal elimination of CO_2, then the $PaCO_2$ will rise and the arterial H+ concentration will rise (by mass action). Increased arterial H+ concentration due to CO_2 retention is called **respiratory acidosis.**

Conversely, if a person is **hyperventilating,** then $PaCO_2$ and H+ concentration will decrease, producing **respiratory alkalosis**.

Ventilation is Regulated by Chemoreceptors

Respiratory rate and tidal volume can increase or decrease over a wide range. At rest, chemoreceptors (Fig 4) located in the periphery and centrally within the CNS provide feedback to regulate these two factors.

Peripheral chemoreceptors are the carotid receptors and aortic bodies. They are stimulated by:

a. decrease in PaO_2 (hypoxia)
b. increase in $PaCO_2$ (respiratory acidosis)
c. decrease in pH within the arterial blood (metabolic acidosis).

Of the two, the **carotid receptor is the predominate input** in controlling respiration.

Central chemoreceptors are widely distributed throughout the brain stem. They **respond to an increase in blood PCO_2. These receptors actually sense H+ concentration in the interstitial fluid of the brain.** They are not affected by changes in arterial pH because the blood brain-barrier is not permeable to H+ or HCO_3-. Instead, CO_2 equilibrates across this barrier, causing a change in the interstitial fluid pH. Because the interstitial fluid and the adjoining cerebrospinal fluid contain little protein, they are not well buffered. Hence **small changes in PCO2 produce large changes in pH in this area**.

Ventilatory Response to Oxygen

PaO_2 must decrease to about 50-60 mm Hg before respiration is increased. It has been suggested that the carotid chemoreceptors (which respond to changes in PaO_2), are designed to protect the organism against hypoxia rather than to regulate respiration. Note that the stimulation to hypoxia is **arterial PO_2 not arterial O_2 content**. That means that individuals **with anemia do not have increased ventilation** because their PaO_2 is normal.

Ventilatory Response to Carbon Dioxide

A very small increase in $PaCO_2$ (2-4 mm Hg) provides a powerful stimulus to increase respiration (doubles alveolar ventilation). What is the physiologic role of this response? Recall that changes in $PaCO_2$ have profound effects on pH. Thus this tight regulation of $PaCO_2$ allows for tight control of acid-base balance. For example, in emphysema patients retention of CO_2 occurs because of the decrease in the elastic recoil. This raises their $PaCO_2$ leading to increased minute ventilation (i.e, “blowing down” the CO_2 in the blood). Of the two sets of receptors involved in this reflex response to elevated $PaCO_2$, the central chemoreceptors are more important accounting for ~70% of the increased ventilation.

Hypoxia (low PO_2) potentiates the effects of CO_2. The response curve is shifted to the left and has a steeper slope. Thus a lower PaO_2 will result in a stronger ventilatory response for the same arterial PCO_2.

Very high levels of carbon dioxide (greater than 70-80 mm Hg) can depress respiration, cause headaches, restlessness, faintness, and even unconsciousness or coma.

Changes in pH without changes in $PaCO_2$

Excess retention or elimination of CO_2 causes respiratory acidosis or alkalosis, respectively. However, many normal and pathological conditions can change arterial H+ levels in which the primary cause is not a change in PCO_2. These conditions are called **metabolic acidosis** (increased H+ concentration) and **metabolic alkalosis** (decreased H+ concentration).

For example, in strenuous exercise, lactic acid is released by the working muscle. The addition of lactic acid to the blood lowers the pH and causes hyperventilation almost entirely by stimulating the peripheral chemoreceptors. Recall that H+ do not cross the blood brain barrier, but CO_2 does and is converted in the interstitial fluid to H+ and HCO_3-.

Predict what happens when arterial H+ concentration is decreased by vomiting (loss of acid from the stomach). Is ventilation increased or decreased? *Answer: The peripheral chemoreceptors will reflexively decrease ventilation to conserve CO_2 in the blood.* Thus the respiratory system compensates for metabolic acidosis by increasing ventilation (hyperventilation) and for metabolic alkalosis by decreasing ventilation (hypoventilation). Notice that maintenance of PCO_2 levels is not as important as maintenance of H+ concentration in the blood. This is because most enzymes of the body function best at physiological pH (pH = 7.4).