GOMEL STATE MEDICAL UNIVERSITY
Normal and Pathological Physiology Department

PHYSIOLOGY OF RESPIRATION

GAS TRANSPORT BY BLOOD. REGULATION OF RESPIRATION.

Lecture 2

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Lecture plan:

1. Gas transport by blood.

2. Regulation of respiration.

a. Localization and structural organization of the respiratory center.

b. Role of gas composition in the regulation of the respiratory center activity.

c. Role of chemoreceptors in the regulation of respiration.

d. Role of respiratory mechanoreceptors in the regulation of respiration.

1. *Gas transport by blood*

O_2 and CO_2 are transferred by blood in two forms:

a) In a free (dissolved) form;

b) In a bound form.

As simple physical solutions O_2 and CO_2 are present in a comparatively small volume (O_2 — 0.3 %, CO_2 — 3.0 %). Actually from blood they can be extracted: O_2 — 60 times and CO_2 — 18 times more, i.e. it testifies to the fact that the basic form of their transmission is the bound one.

However, the state of physical dissolution of O_2 and CO_2 is of high significance. To contact these or those substances, gases should be first dissolved in blood plasma, i.e. each molecule of O_2 or CO_2 is dissolved for a while before it reaches erythrocytes.

O_2 transport. A large amount of O_2 is transported by blood as a chemical compound with hemoglobin (Hb) — ***oxyhemoglobin*. *1g of hemoglobin can bind 1.34–1.36 ml of O_2.***

The maximum amount of oxygen which can combine chemically with a given amount of hemoglobin in the blood is named the ***oxygen capacity of blood*** and does not include oxygen dissolved in plasma. It is equal to **18-22 vol. %** (percent by volume).

The values of the oxygen capacity of blood depends on the Hb concentration. For example, if the concentration of Hb is 140 g/L, the oxygen capacity of blood is:

1.34 mL O_2 × 140 g/L = 187.6 mL ≈19 vol. % (1 liter of blood contains 190 mL of oxygen).

However, the degree of Hb oxygenation first of all depends on the partial pressure of O_2 in a medium in which blood contacts. This dependence is expressed by the so-called ***oxyhemoglobin dissociation curve*** (Figure).

The oxyhemoglobin dissociation curve shows the percentage of Hb bound with O_2 at different partial pressures of O_2.There are 3 parts on the curve: pO_2 from 0 to 10mm Hg. — directly proportional dependence, from 10 to 60 mm Hg— saturation is very fast, from 60 to 90 mm Hg — saturation is almost not changed.

During O_2 diffusion in the lungs, the partial pressure of O_2 in the blood is close to pO_2 in the alveoli making 96 mm Hg. Under this partial pressure approximately 97 % of HbO_2 is formed.

Even if pO_2 in arterial blood decreases to 60 mm Hg, Hb oxygenation drops down insignificantly and HbO_2 is 90 %. It has an important physiological value: with age or in pulmonary diseases pO_2 in alveolar air can decrease and if its level does not decrease below 60 mm Hg, oxygenation is reduced insignificantly and tissues are sufficiently supplied with O_2.

The abrupt part of the curve corresponds to the partial pressure of O_2 typical for tissues (35 mm Hg and lower). It creates a favorable situation for the return of O_2 to tissues.

The parameter of the affinity of Hb to O_2 is the partial pressure of O_2 in which half of Hb is bound with O_2 (p50). Normally, it is equal to 26–28 mm Hg. Increased affinity of Hb to O_2 results in a decrease of p50, and vice versa.

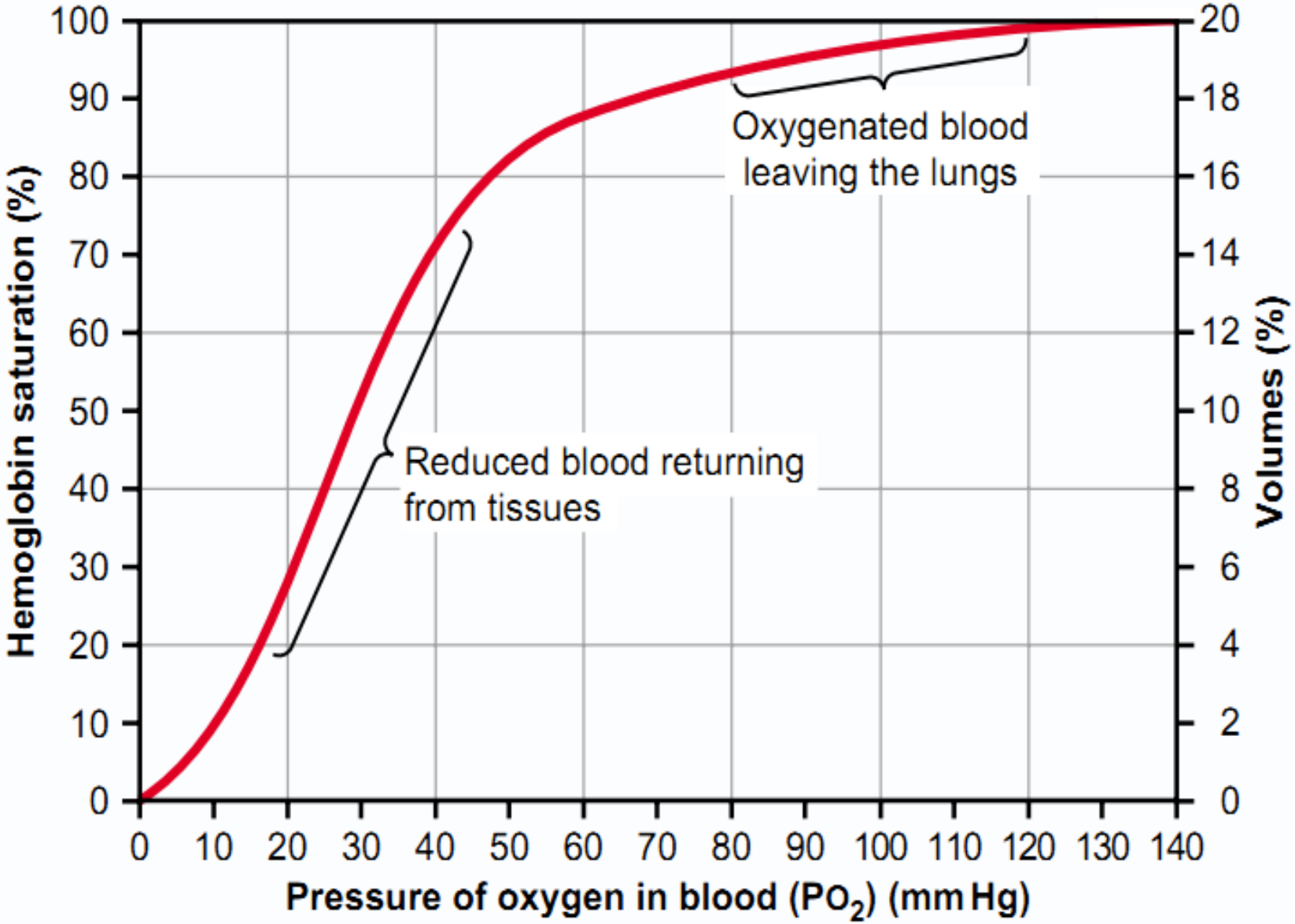


Figure — Oxyhemoglobin dissociation curve

HbO_2 dissociation in tissues depends on the intensity of oxidative processes: in intensively working tissues and organs HbO_2 dissociation increases, in less intensively working tissues and organs it decreases.

The factors which influence the ***HbO_2 dissociation curve (the affinity of Hb to O_2).***

1. Temperature. If the temperature goes up, the slope of the HbO_2 dissociation curve descends and ***shifts to the right***, i. e. HbO_2 dissociation is increased (Figure).

2. **In a pH** shift towards its decrease, i. e. H^+ increase, the curve of HbO_2 dissociation ***shifts to the right***, i. e. HbO_2 dissociation is increased (Figure).

3. **pCO_2** in the blood. The higher pCO_2 is, the higher HbO_2 dissociation is (***the curve shifts to the right***).

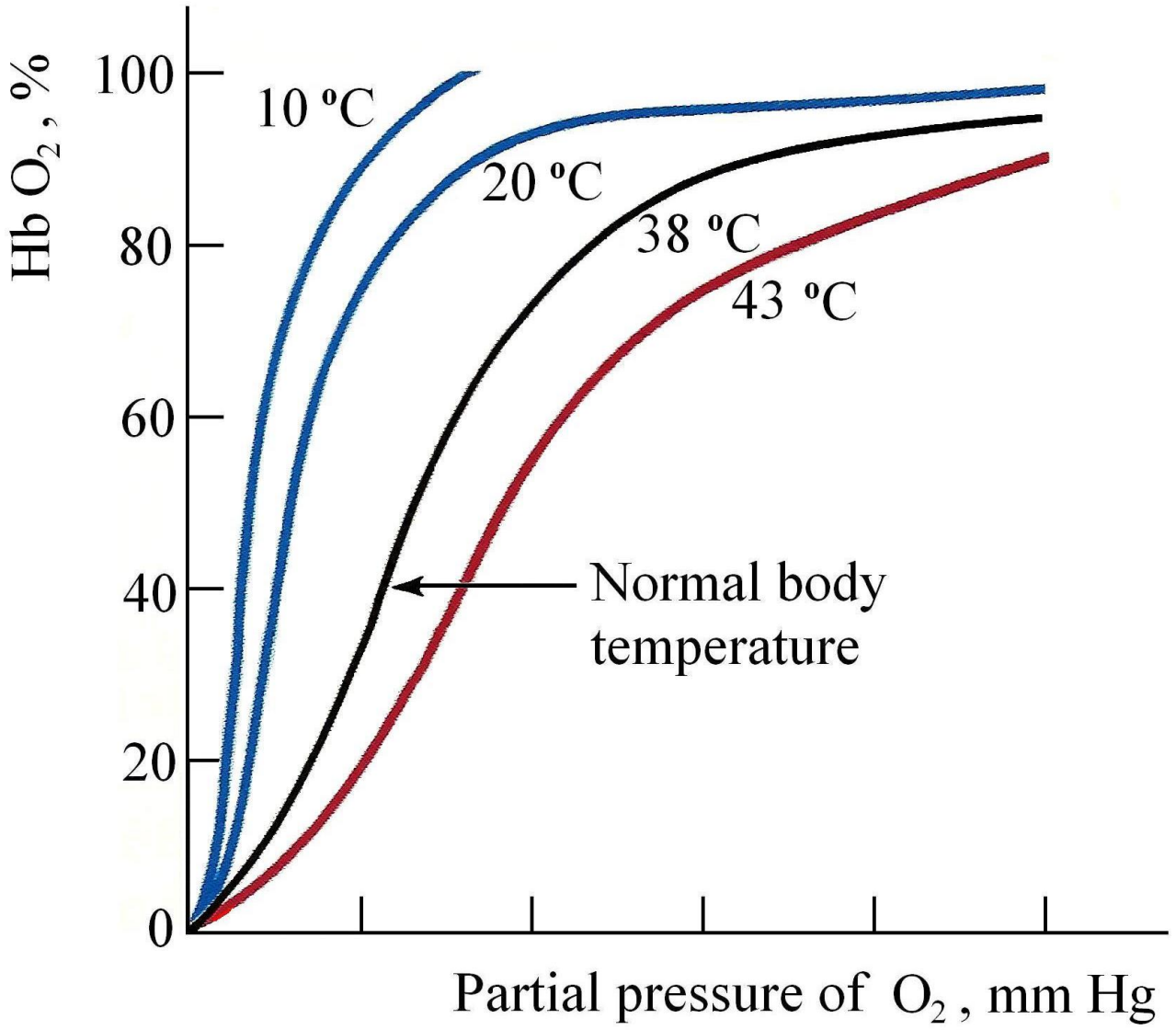


Figure — Effects of temperature on the hemoglobin dissociation curve

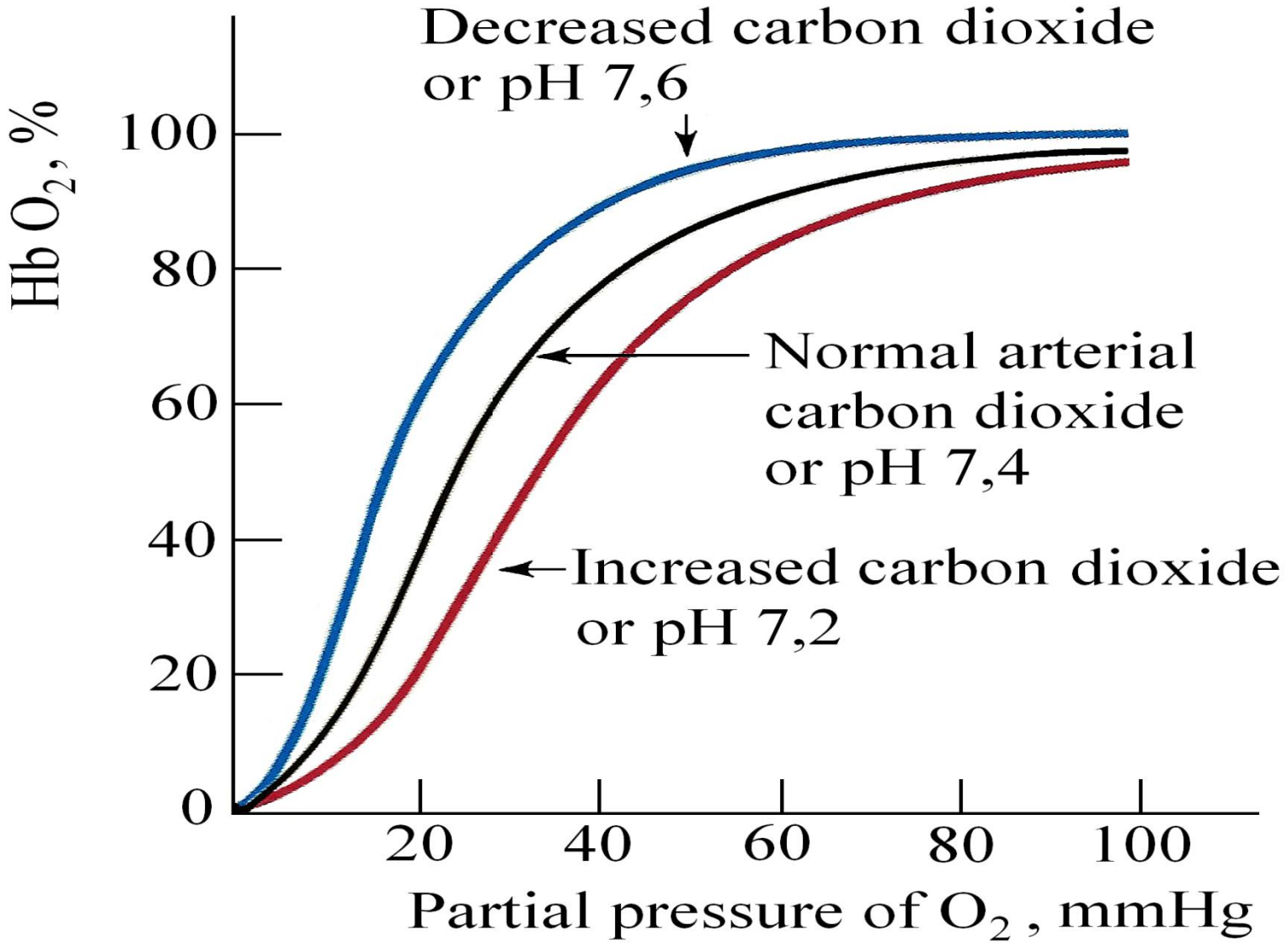


Figure — Effects of partial pressure of CO_2 and blood pH on the hemoglobin dissociation curve

These factors reduce Hb affinity to O_2.

Any changes of the given factors have an important value for tissue provision with oxygen, mainly those functioning more intensively at the moment.

E. g.: in a working muscle t° and CO_2 rise and pH decreases, i. e. factors promoting HbO_2dissociation and providing the optimal oxygen nutrition of the muscle, appear.

In hypoxia (low pO_2 in tissues) the synthesis of ***2,3-diphosphoglycerate,*** which reduces Hb affinity to O_2 increased in erythrocytes. This results in HbO_2 dissociation and O_2 return to tissues.

The curve of ***HbF (fetus)*** dissociation, due to its higher affinity to oxygen is ***shifted leftwards*** as compared with ***HbA (adults).***

Arterial blood contains approximately 20 vol. % of O_2, and venous blood — 12 vol. %. For the evaluation of O_2 utilization by tissues **the oxygen utilization coefficient** (UC) is used.

$$O_2\ UC = \frac{(O_2\ \text{vol. \%. in arterial blood} - O_2\ \text{vol. \%. in venous blood}) \times 100}{O_2\ \text{vol. \%. in arterial blood}}$$

The **oxygen utilization coefficient** in a person at rest is **30–40 %.** In physical activity it increases **up to 50–60 %.**

CO_2 transport by blood

It is transported:

1) In physically dissolved state.

2) In the form of chemical compounds:

a) of acidic salts of carbonic acid;

b) of carbohemoglobin.

In tissues. CO_2 formed in tissues passes to capillary blood (Figure**)**.

In erythrocytes:

$CO_2 + H_20 \rightarrow H_2CO_3$

The process is accelerated by 20,000 times by ***carbonic anhydrase***. This process proceeds only in erythrocytes (there is no carbonic anhydrase in plasma). In the capillaries of the lungs this enzyme, on the contrary, catalyzes the breakdown of H_2CO_3.

In erythrocytes part of CO_2 is connected with hemoglobin:

$CO_2 + Hb \rightarrow$ Carbohemoglobin

Since as a result of these processes the partial pressure of CO_2 in erythrocytes does not increase, all new portions of CO_2 diffuse into erythrocytes. At the same time, the concentration of HCO_3^- ions in erythrocytes increases, some part of which go to blood plasma. Their place in erythrocytes is taken by Cl^- ions whose negative charges are equalized by positive K^+ ions. In plasma the volume of bicarbonate ($NaHCO_3$) increases; in erythrocytes — $KHCO_3$.

In pulmonary capillaries $KHbO_2$ releases O_2 and transforms into KHb. Carbonic acid, being a stronger acid, expels K^+ from it:

$$KHbO_2 + H_2CO_3 \rightarrow HHb + O_2 + KHCO_3.$$

Therefore, the transformation of HbO_2 into hemoglobin is accompanied by the increased ability of blood to bind CO_2. In such a state CO_2 is transferred to the lungs.

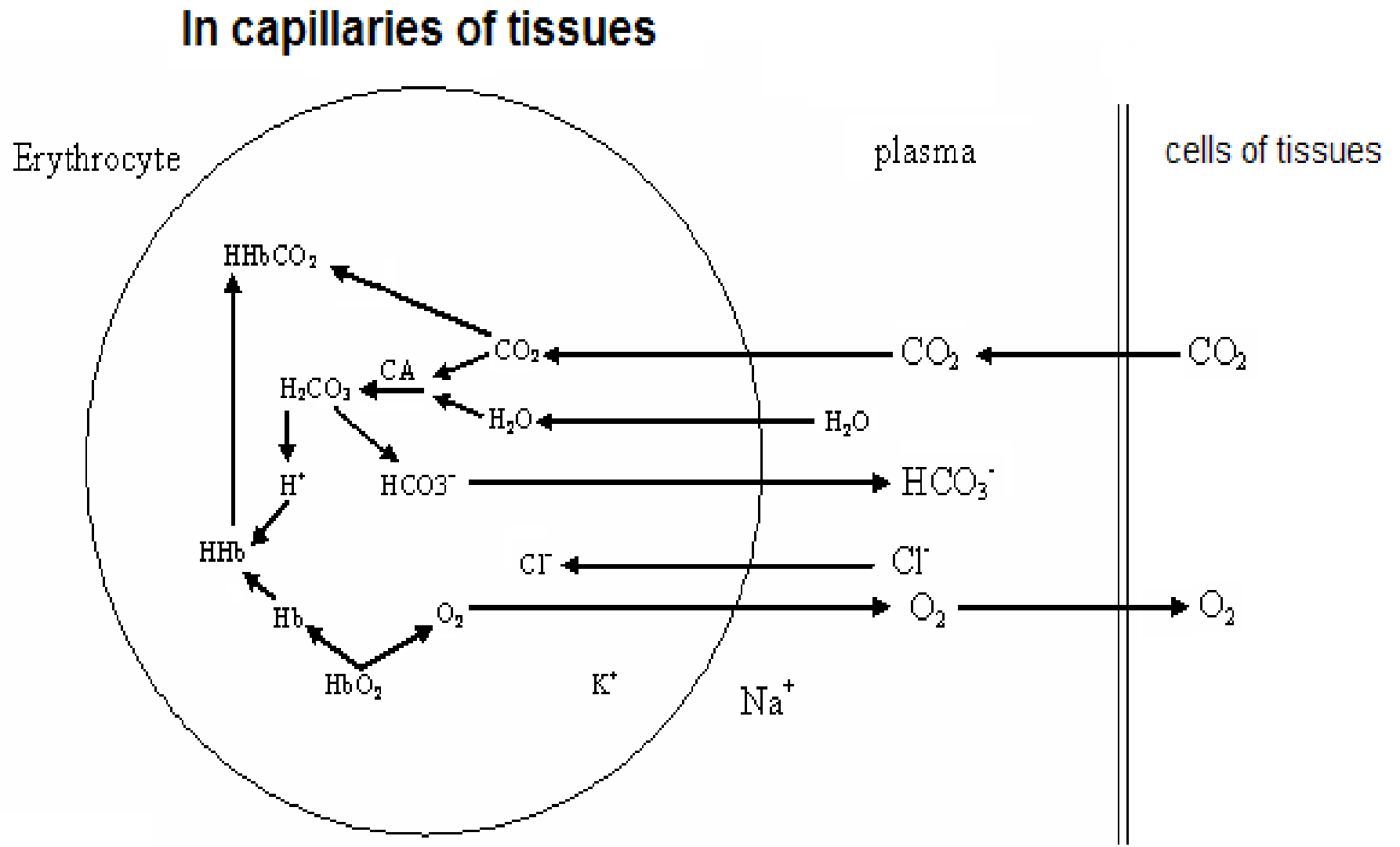


Figure — CO_2 transport (scheme)

In the lungs. From carbohemoglobin CO_2 is detached, and simultaneously oxyhemoglobin is formed. Oxyhemoglobin is a stronger acid than carbonic acid, therefore, HbO_2 expels K^+ from bicarbonates and is transported as a $KHbO_2$ salt. This results in the formation of H_2CO_3 in erythrocytes (***carbonic anhydrase***).

HCO_3^- ions enter erythrocytes and Cl^- ions enter blood plasma where the volume of Na^+ bicarbonate decreases, and CO_2 diffuses into the alveoli.

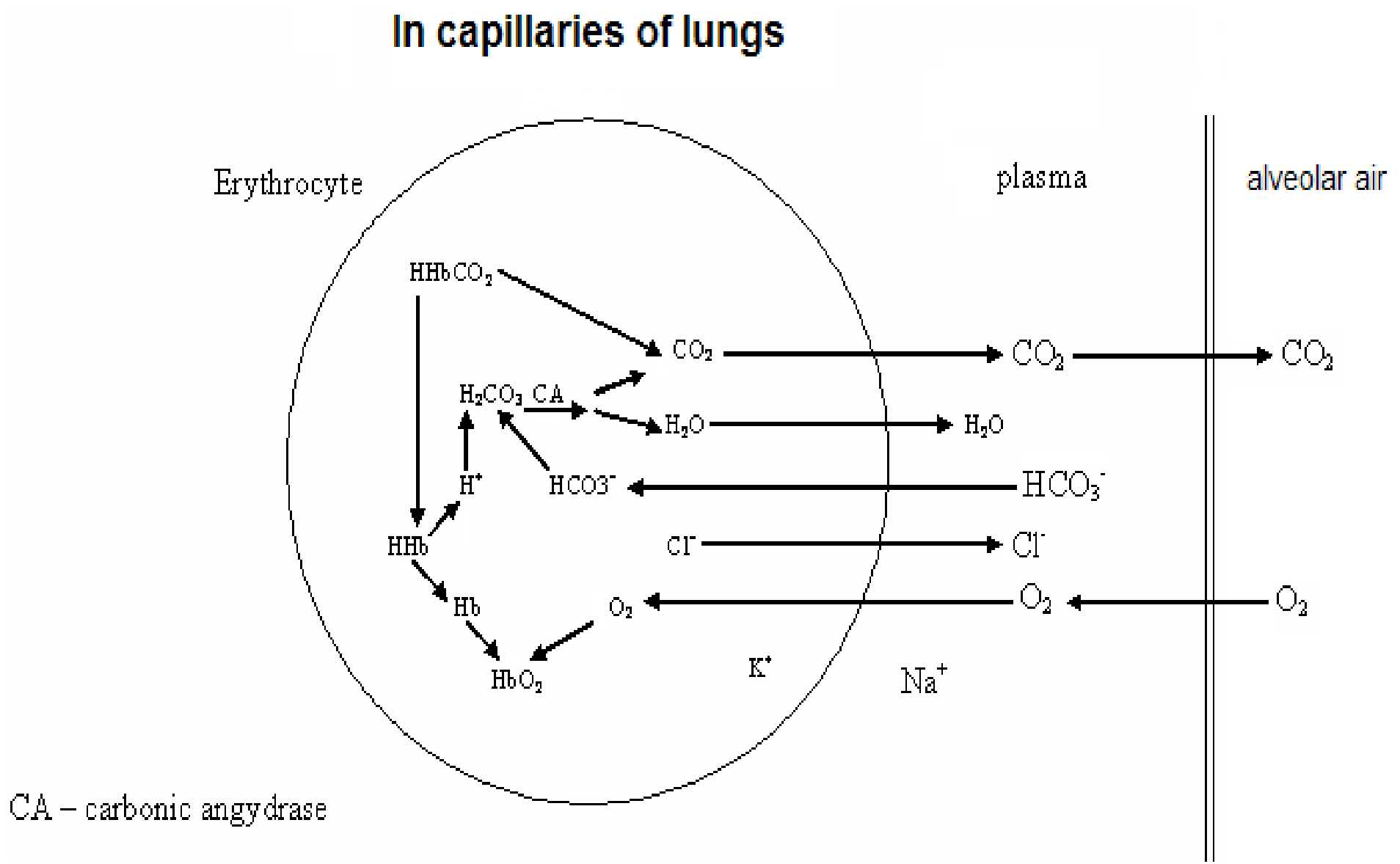


Figure — CO_2 transport (scheme)

2. Regulation of respiration

a. Localization and structural organization of the respiratory center

Somatic nerve fibers innervate respiratory muscles. Their deinnervation results in apnea. The motoneurons of intercostal and abdominal muscles are located in the ***thoracic segments of the spinal cord.*** The motoneurons innervating the diaphragm are located in ***III–IV cervical segments***. After dissection of the spinal cord at the level of the superior cervical segments respiratory movements stop. If the spinal cord is dissected at the level of the inferior cervical segments (below III–IV) — the movements of the diaphragm continue, those of intercostal muscles stop (Figure).

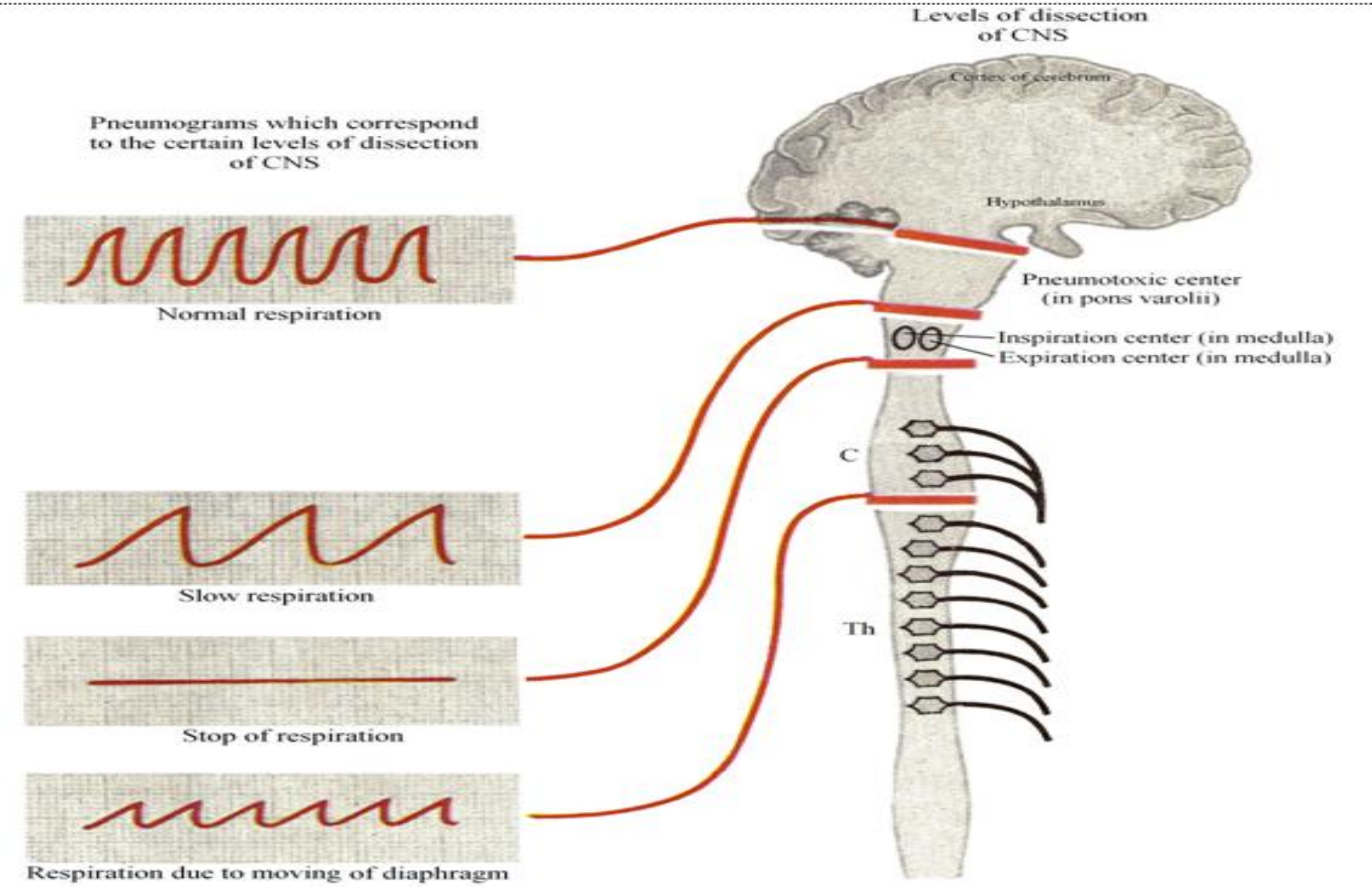


Figure — Influence of dissection of different levels of the central nervous system on respiration

Dissection of the brain between the midbrain and medulla does not change respiration in a person at rest. It is indicative of the location of the ***respiratory center*** in the **medulla and pons varolii**. Dissection of the brain between the medulla and pons varolii does not stop respiration but it differs from normal. It means that the major structures of the respiratory center are located in the medulla.

These structures form **the bulbar respiratory center**, the damage of which results in arrested respiration.

Therefore, the centers of the brain participating in the regulation of respiration are located in the **medulla**.

There are 2 basic groups of respiratory neurons:

1. ***Inspiratory***.
2. ***Expiratory***.

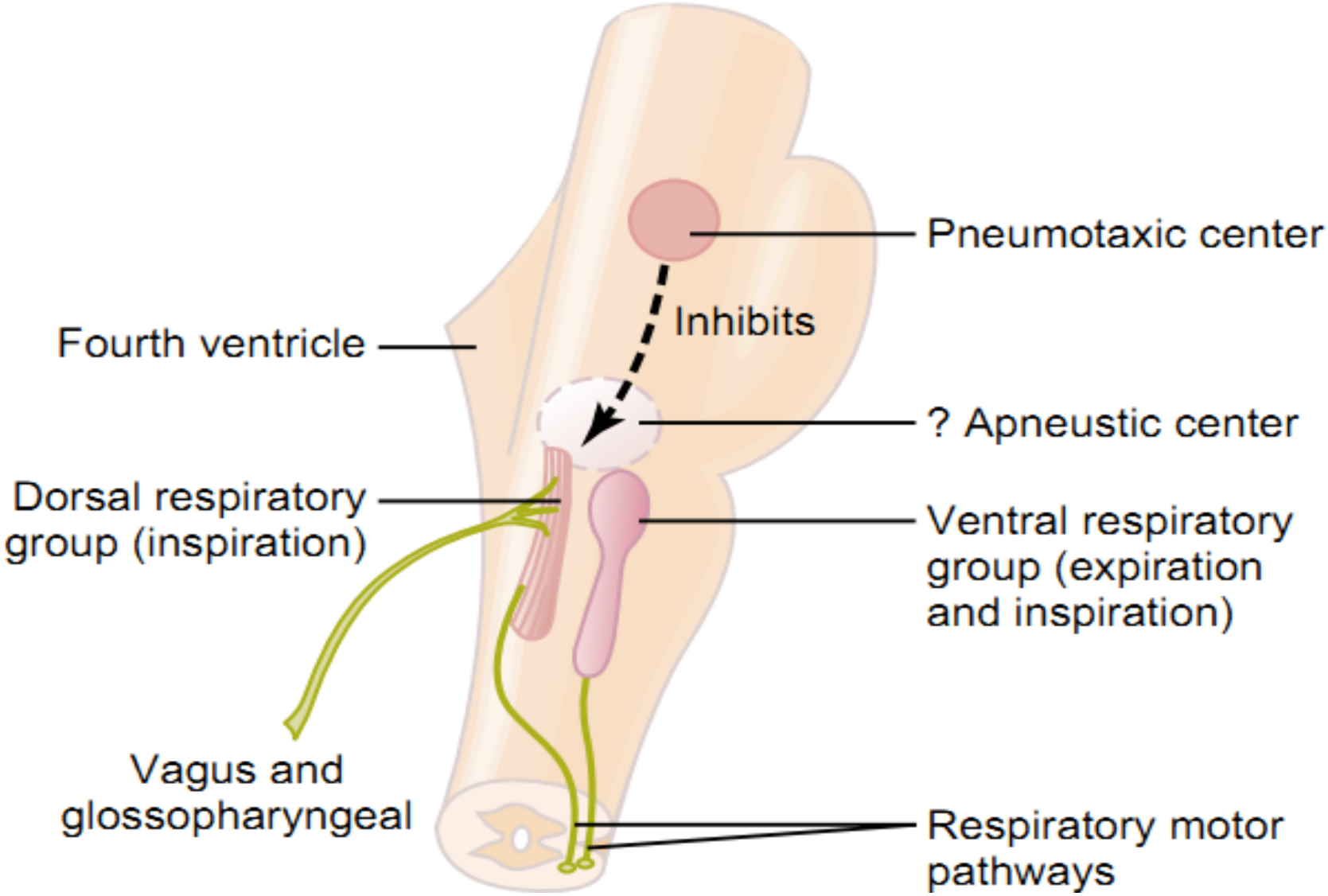


Figure — Organization of respiratory center

Localization of respiratory neurons. In both the halves (left and right) of the medulla 2 groups of respiratory neurons are situated: dorsal and ventral respiratory nuclei.

1. ***The dorsal respiratory nucleus*** contains mainly inspiratory neurons, whose axons are directed to the diaphragm nuclei of the cervical part of the spinal cord. Collaterals from them go to the ventral respiratory nucleus where they form excitant synapses on expiratory neurons and inhibit their activity.

As for expiratory neurons, their number in the dorsal respiratory nucleus is insignificant. This part, i.e. the dorsal respiratory nucleus where mainly the inspiratory neurons are located is called the **«inspiration center»** (Figure).

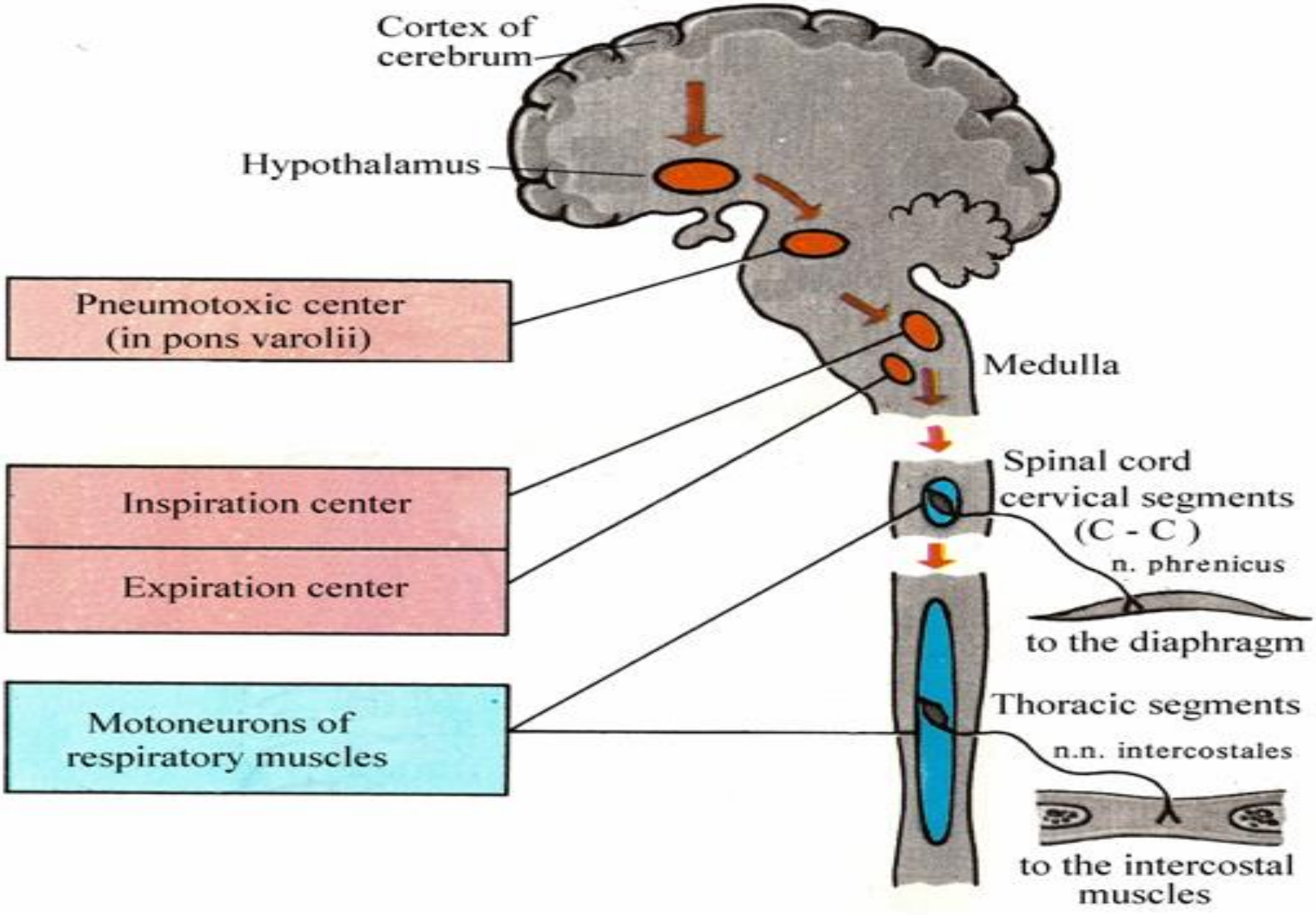


Figure — Respiratory center (its components) and efferent nerves

2. ***The ventral respiratory nucleus*** contains inspiratory and expiratory neurons. This part is called the **«expiration center».** The expiratory neurons send impulses:

1) to the motoneurons of the intercostal and abdominal muscles situated in the thoracic and lumbar parts of the spinal cord;

2) partially to the motoneurons of the diaphragm.

At the same time, the respiratory neurons are located both in the reticular formation of the medulla and in the pons varolii.

b). Role of gas composition in the regulation of the respiratory center activity

The functional activity of the respiratory center is determined by the **partial pressure of gases and pH in the blood**. **The leading role here is played by the partial pressure of CO_2.**

In general conditions the human body is supplied with sufficient volume of O_2. Even in conditions when pO_2 in alveolar air can decrease to 60–70 mm Hg, the organism does not develop significant disorders. pCO_2 is maintained at a relatively constant level providing the functional activity of the respiratory center.

Changes of gas strain in the blood influences the activity of the respiratory center, the signs of which are changes of:

1. **Respiration rate.**
2. **Respiration depth.**
3. **Lung ventilation.**

It can result in:

1) maintenance of normal CO_2 volume in the blood (*normocapnia*);

2) increase of CO_2 (*hypercapnia*);

3) decrease of CO_2 (*hypocapnia*);

4) normal O_2 volume (*normoxia*);

5) deficiency of O_2 in tissues (hypoxia);

6) deficiency of O_2 in blood (*hypoxemia*).

As a rule, there is no increased amount of O_2 in the blood.

Normocapnia is accompanied by normal respiration (***eupnea***).

Simultaneous hypoxia and hypercapnia cause ***asphyxia (dyspnea)***.

In hypercapnia or low pH level (acidosis) — lung ventilation is increased due to the depth of respiration (basically) and its frequent rate ***(hyperpnea)***.

Hypocapnia or high pH level (alkalosis) results in decreased lung ventilation and ***apnea***.

Hypoxia develops in individuals who ascend to high altitudes, have blood circulation or blood composition disorders, or do hard physical work.

c). Role of chemoreceptors in the regulation of respiration

In arterial blood the partial pressure of O_2, CO_2, and pH depends on lung ventilation.

But, in its turn, they are factors influencing the intensity of this ventilation, i. e. they influence the activity of RS.

The Frederico test with cross-circulation (Figure). In two dogs the carotid arteries and jugular veins were cross-connected, the vertebral artery being ligated. As a result of the experiment, the head of the first dog was supplied with the bloodstream of the second dog, and vice versa. The tracheal pinching in the first dog causing asphyxia resulted in hyperpnoea in the second dog. In the first dog apnea occurred despite the increase of pCO_2 and decrease of pO_2.

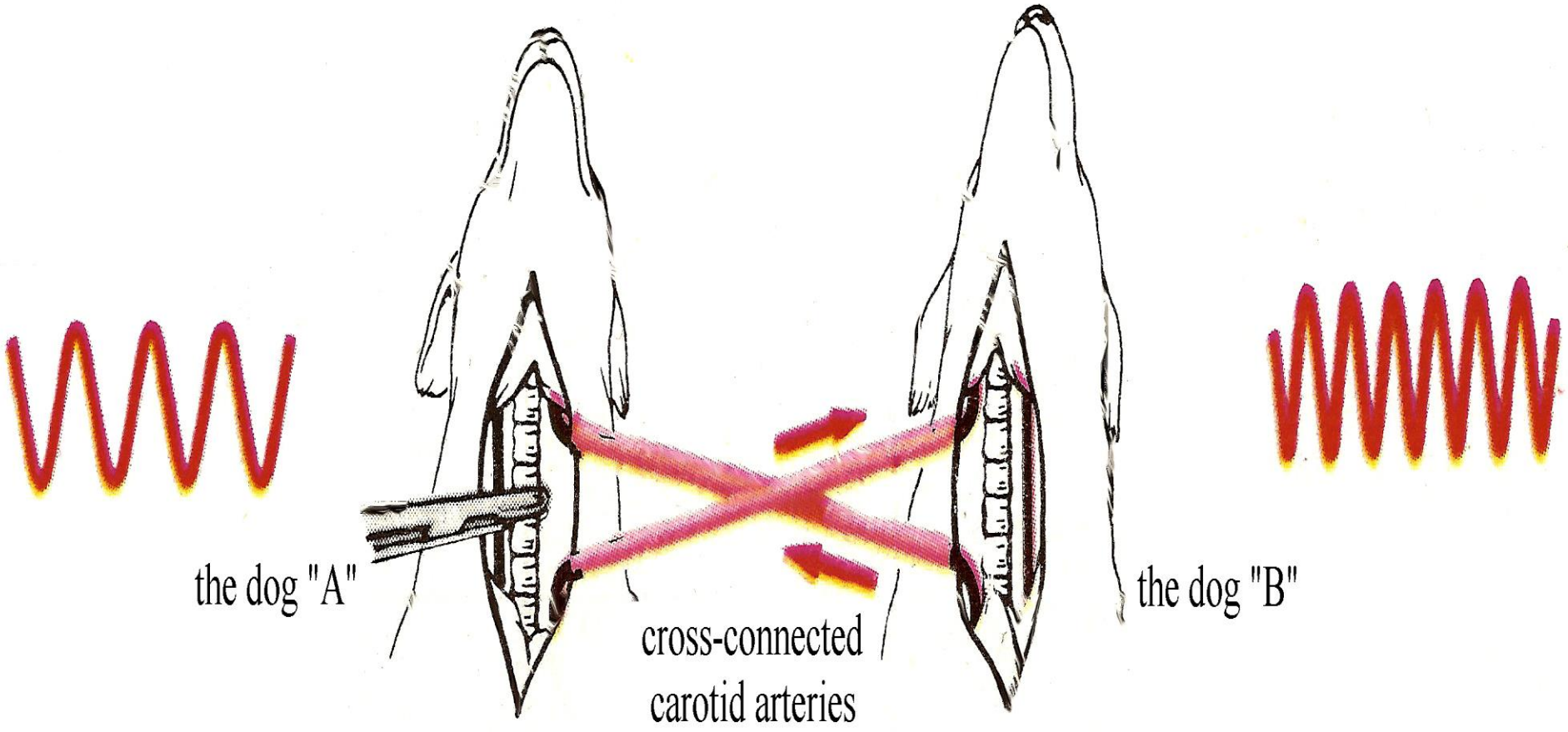


Figure — The Frederico test with cross-circulation

Notes: Pinching of the trachea of the dog «A» courses hyperpnoea in the dog «B»; hyperpnoea of the dog «B» courses decreasing of ventilation rate in the dog «A».

Such changes of respiration were observed because the carotid artery of the first dog received the blood from the second dog in which, pCO_2 in the blood was decreased due to hyperventilation. This influence is carried out through special ***chemoreceptors***. There are two kinds of chemoreceptors according to their localization:

1. Central (bulbar) — they are located in the *central nervous system, in the medulla*.

2. Peripheral (arterial) — they are located *in the blood vessels*.

From these receptors signals about the gas composition of blood come to the respiratory center.

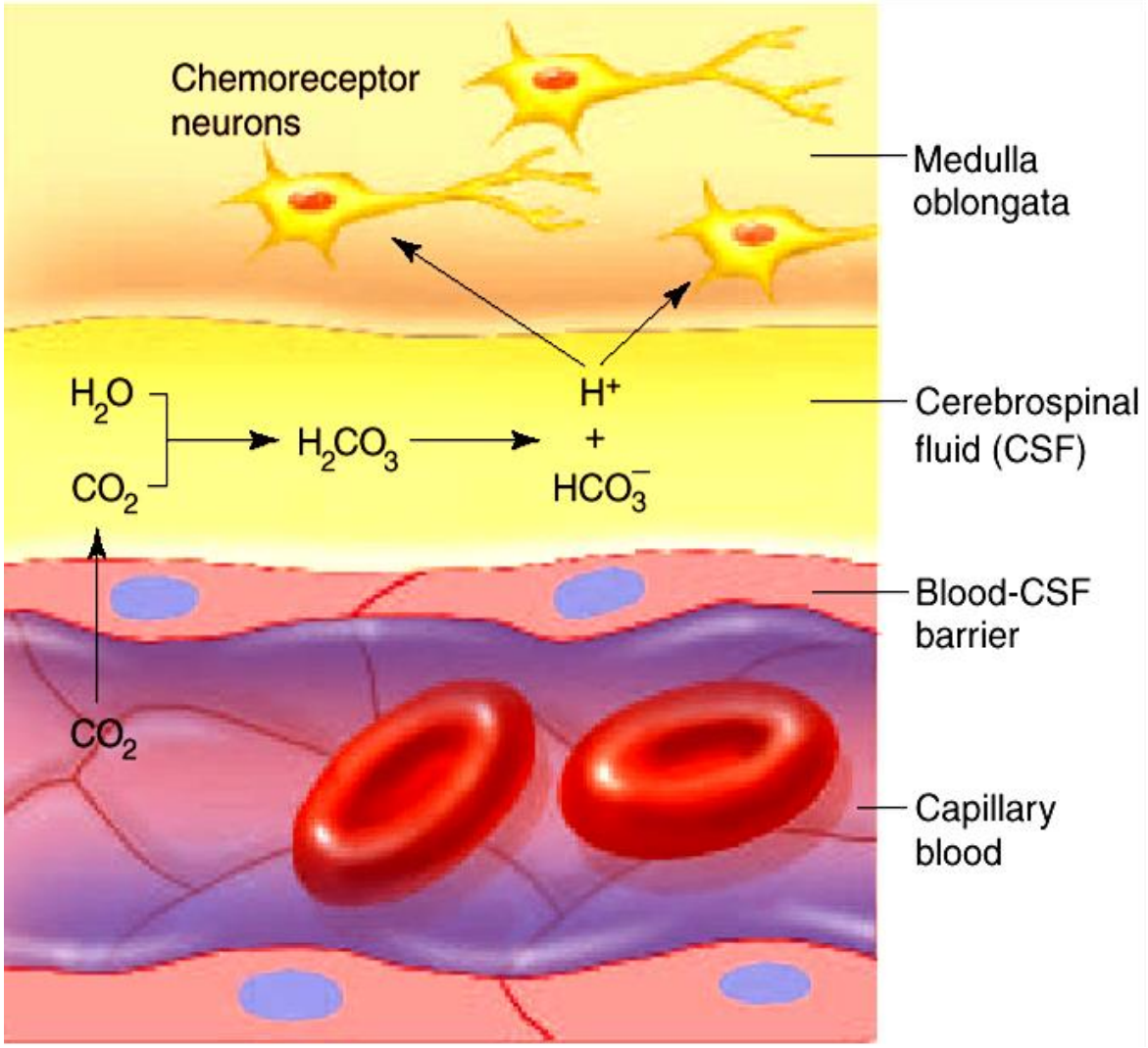
The role of the central chemoreceptors.

The central chemoreceptors are located in the **medulla** and detect the pH changes of nearby cerebrospinal fluid that are indicative of altered oxygen or carbon dioxide concentrations. Perfusion of the medulla portion within the area of the given receptors with ***solution of lower pH*** results in rapid intensification of respiration, and vice versa.

In natural conditions the central chemoreceptors are constantly stimulated by H^+. The concentration of H^+ in the blood depends on CO_2 strain in arterial blood. **Decreased pH level by 0.01 induces increased lung ventilation by 4 L/min.**

At the same time, the central chemoreceptors respond to the changes of pCO_2 but to a lesser degree than to the changes of pH. It is presumed that the basic chemical factor influencing the central chemoreceptors is the H^+ amount in the intercellular fluid of the brain stem and the action of CO_2 is mediated by the formation of these ions.

Figure — Mechanism of H^+ increase in cerebrospinal fluid



H^+ ions from blood does not cross blood-brain barrier, but CO_2 easily crosses this barrier and enters CSF, where it is converted to H^+ and HCO^{3-} ions (by carboanhydrase).

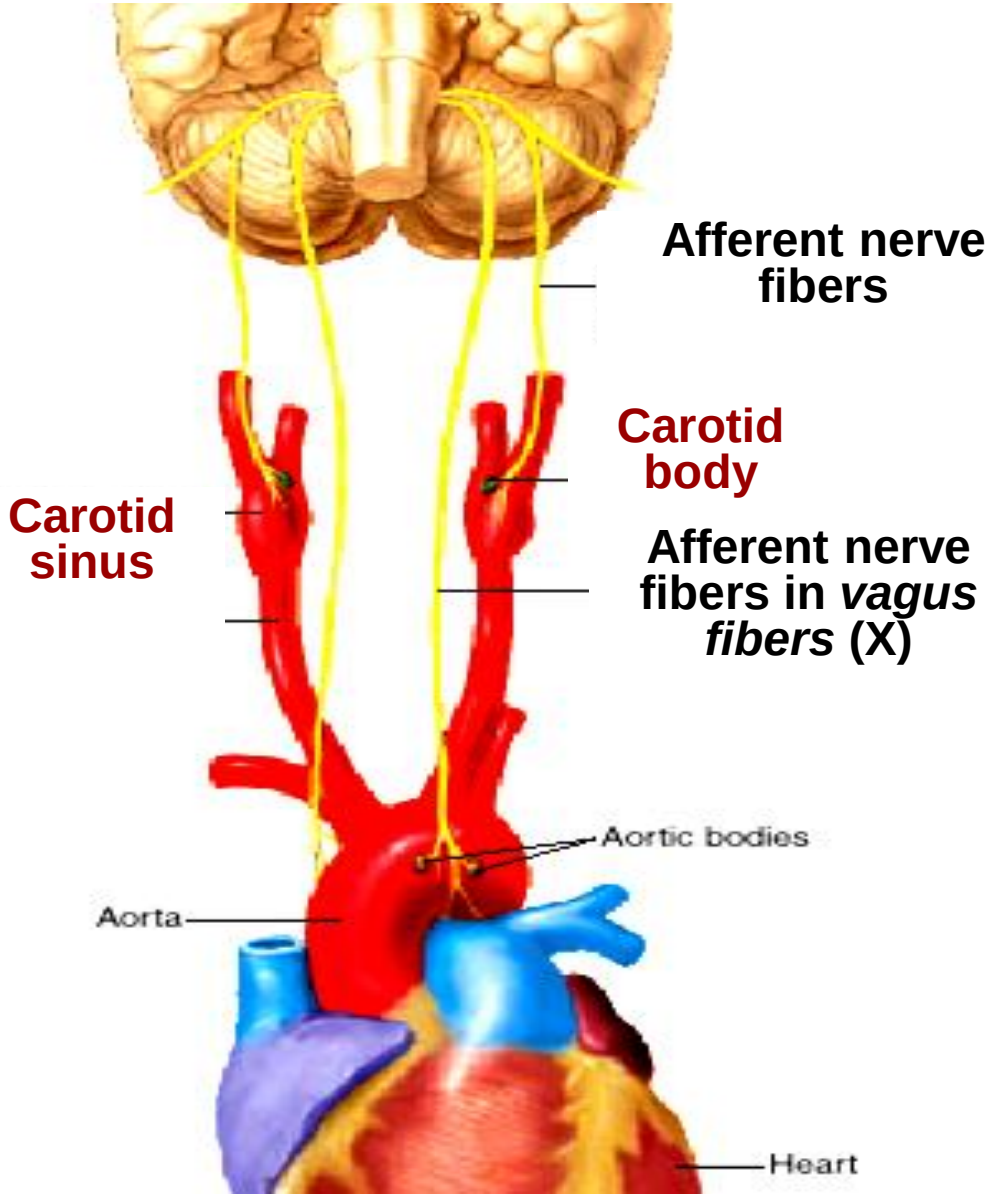
The role of arterial (*peripheral)* chemoreceptors. O_2, CO_2, and H^+ can influence the central nervous system not only centrally but also by exciting the peripheral chemoreceptors.

The most important of them are:

1. ***The carotid bodies*** located in the vicinity of the division of the common carotid artery into internal and external carotid arteries.

2. ***Aortal bodies***.

Figure — Peripheral chemoreceptors



Afferent nerve fibers begins from receptors of aortic and carotid bodies:

from aortic arch - fibers of vagus nerve (X), from the carotid body – fibers of glossopharyngeal nerve (IX).

The chemoreceptors of the indicated zones are excited in ***increased pCO_2 and decreased pO_2 and pH levels.*** The influence of O_2 on the respiratory center is mediated only by the peripheral chemoreceptors.

Thus, the neurons of the respiratory center remain activated by the impulses coming from the central (bulbar) and peripheral (arterial) chemoreceptors reacting to changes of the three parameters of arterial blood:

1. Low pO_2 (***hypoxemia***).
2. High pCO_2 (***hypercapnia***).
3. Low pH (***acidosis***).

The main stimulant of respiration is *hypercapnia*. The higher pCO_2 is (pH is also connected with it), the more frequent lung ventilation is.

However, the strongest stimulant of the central respiratory mechanism is the combined action of hypoxemia and hypercapnia (and acidosis connected with it).

d). Role of respiratory mechanoreceptors in the regulation of respiration

In changes of the respiratory phases, i.e. periodic activity of the respiratory center the essential role is played by the ***mechanoreceptors (stretch receptors)*** (Figure), located in the smooth muscles of the walls of the trachea, bronchi, bronchioles, for which various degree of excitability is typical. Some of them (approximately 1/2) are ***low-threshold*****.** They are intensively excited during breathing. Impulsion from them is strengthened in inspiration and reduced in expiration. The other muscles are ***high-threshold,*** they are excited only in inspiration.

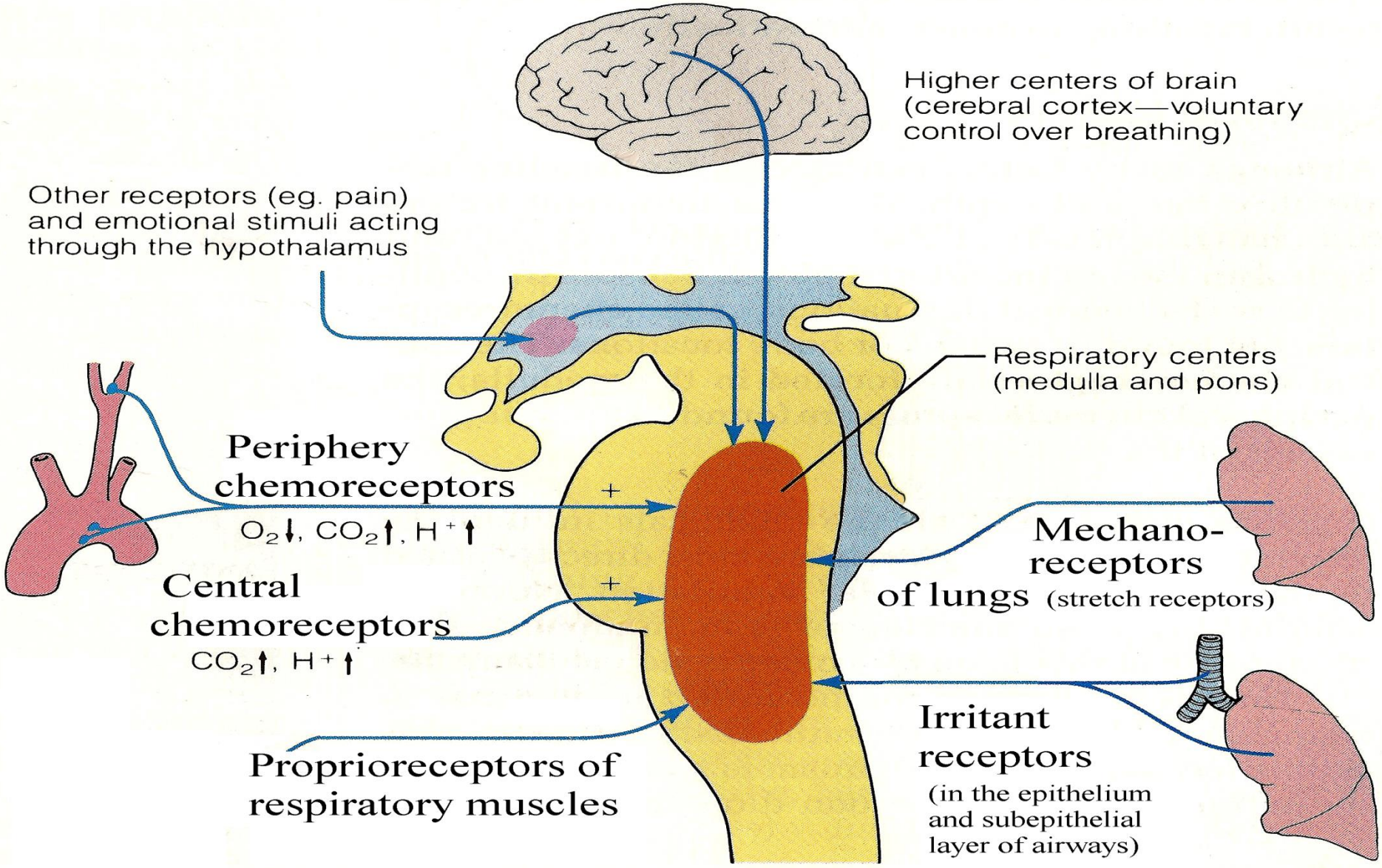


Figure — Neural and chemical influences on the respiratory center in the medulla

During inhalation, as a result of lung expansion stretch receptors get excited. Afferent fibers from these receptors go in the structure of n. vagus into the dorsal respiratory nucleus of te medulla (inspiratory center) and inhibit the activity of inspiratory neurons. The act of inspiration is inhibited.

This reflex provides a change of the phases of the respiratory cycle and is called the **inspiration-inhibitory reflex.** For the first time it was described by Hering and Breuer and received the name of the Hering-Breuer reflex.

The physiologic value of this reflex is the limitation of the respiratory movements. Due to this, the conformity of the depth and frequency of respiration to the conditions of the body functions at the present moment is reached and receptors interfere lung overdistension.

The role of the Hering-Breuer reflex is relatively insignificant in a person being at a state of relative rest. The value of this reflex is extremely great in hyperpnea.