REGULATION OF RESPIRATION

INTRODUCTION

Respiration is a reflex process.

But it can be controlled voluntarily for a short period of about 40 seconds.

However, by practice, breathing can be withheld for a long period.

At the end of that period, the person is forced to breathe.

Respiration is subjected to variation, even under normal physiological conditions.

For example, emotion and exercise increase the rate and force of respiration.

But the altered pattern of respiration is brought back to normal, within a short time by some **regulatory mechanisms in the body.**

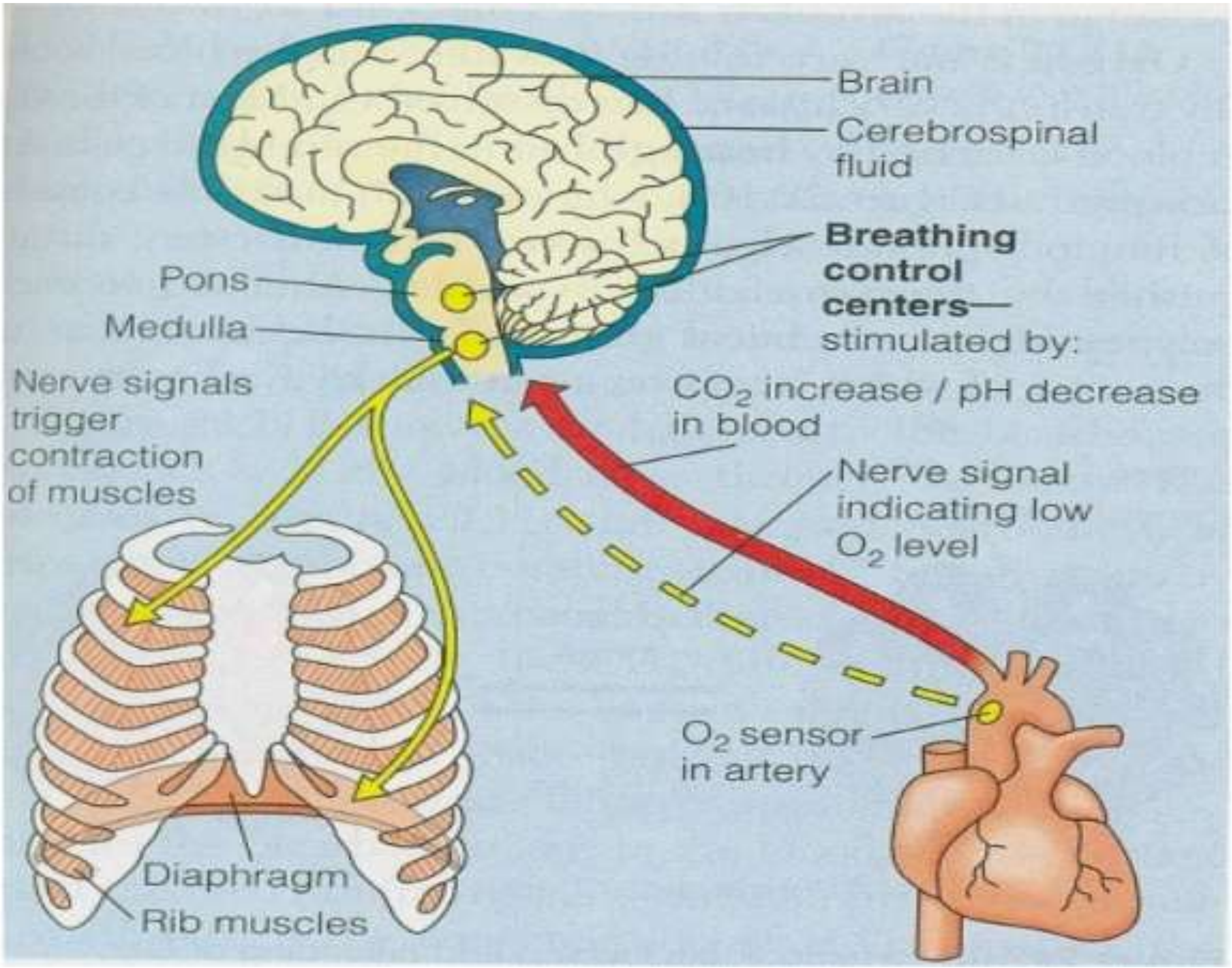
Normally, quiet regular breathing occurs because of two regulatory mechanisms:

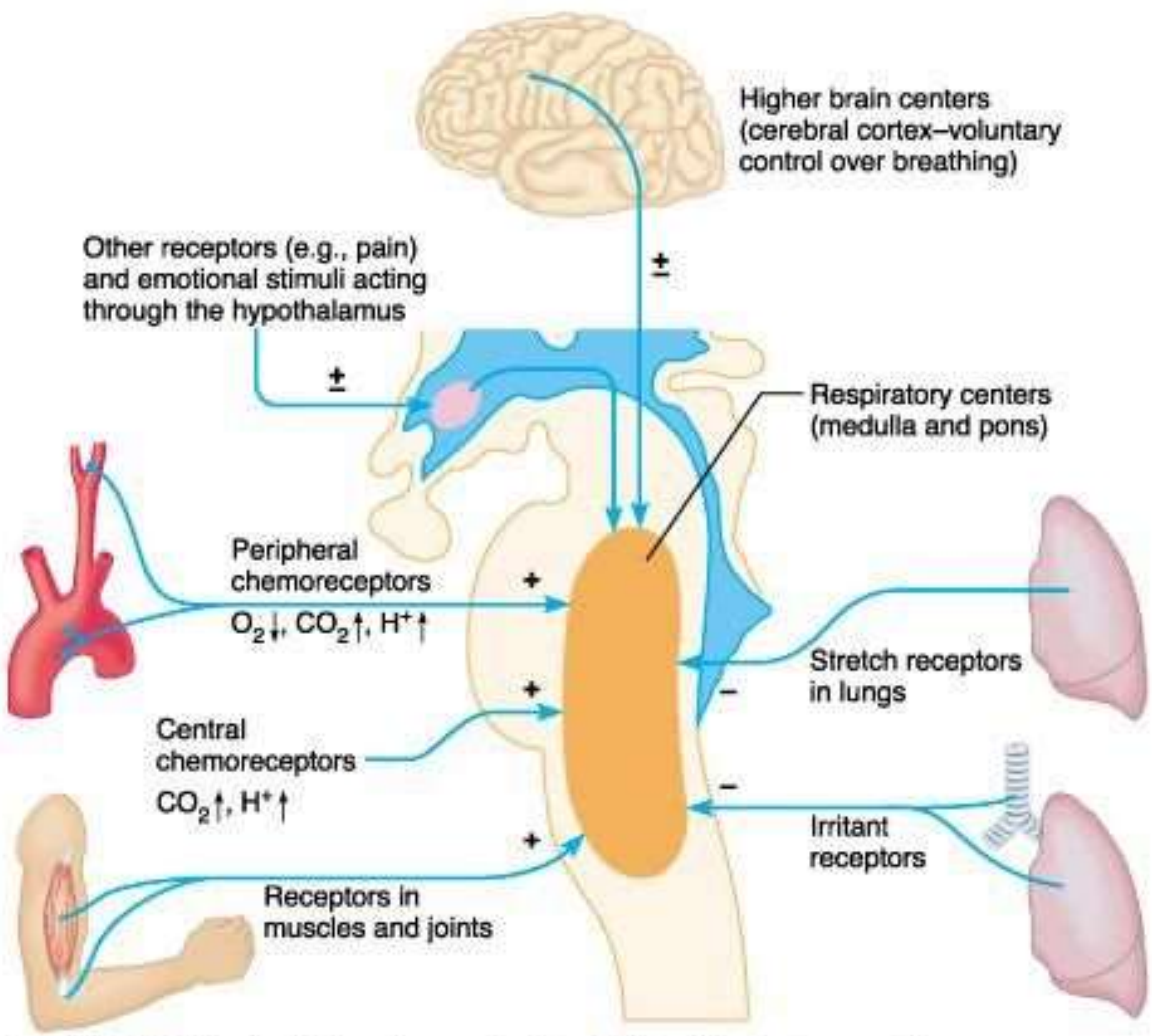
1. **Nervous or neural mechanism**
2. **Chemical mechanism.**

NERVOUS MECHANISM

Nervous mechanism that regulates the respiration includes:

1. **Respiratory centers**
2. **Afferent nerves**
3. **Efferent nerves**




Higher brain centers
(cerebral cortex–voluntary
control over breathing)
±
Other receptors (e.g., pain)
and emotional stimuli acting
through the hypothalamus
±
Respiratory centers
(medulla and pons)
Peripheral
chemoreceptors
$O_2\downarrow$, $CO_2\uparrow$, $H^+\uparrow$
+
Stretch receptors
in lungs
−
+
Central
chemoreceptors
$CO_2\uparrow$, $H^+\uparrow$
−
Irritant
receptors
+
Receptors in
muscles and joints

RESPIRATORY CENTERS

Respiratory centers are group of neurons, which **control the rate, rhythm and force of respiration.**

These centers are bilaterally situated in **reticular formation of the brainstem** .

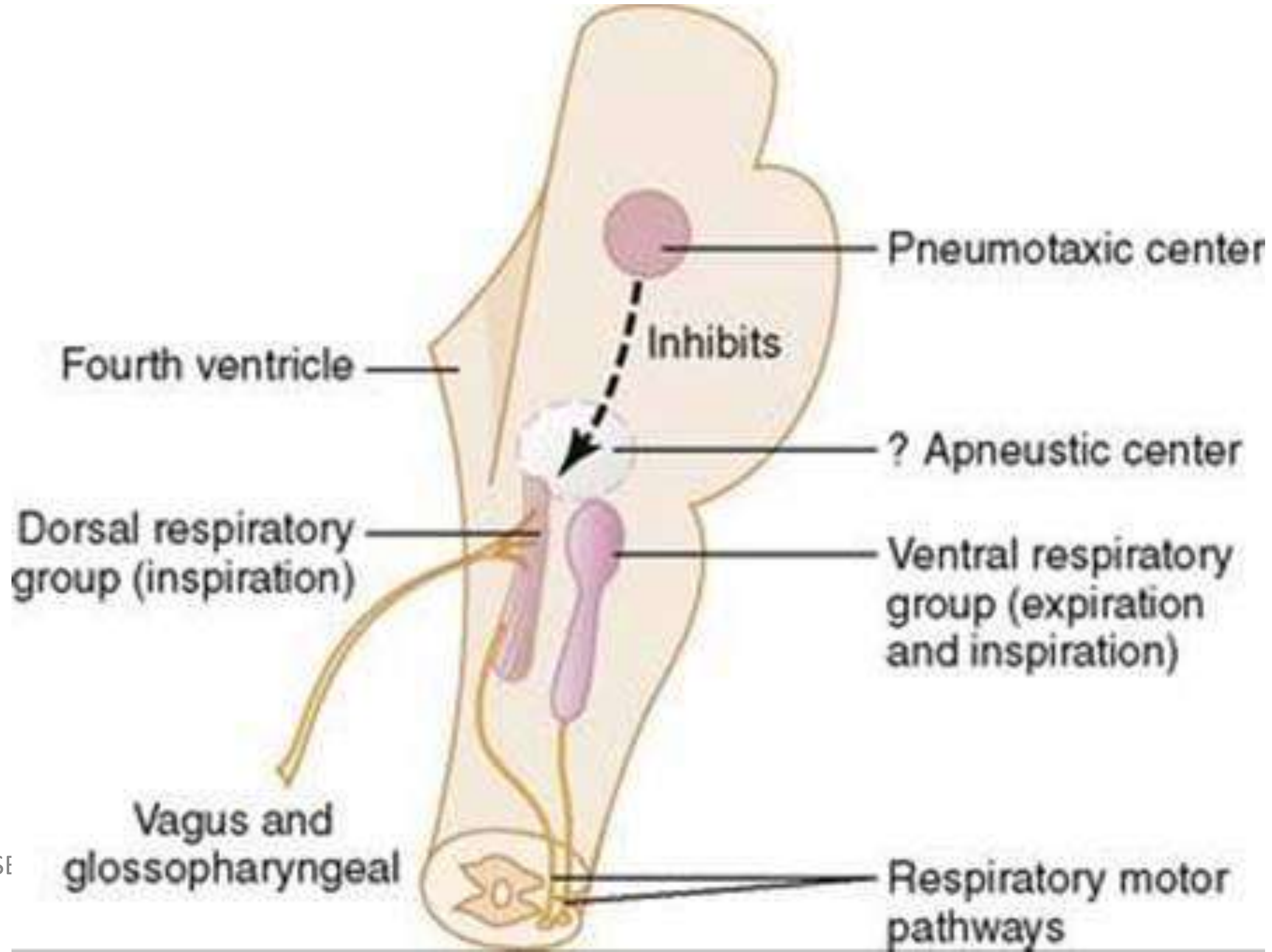
Depending upon the situation **in brainstem**, the respiratory centers are classified into two groups:

A. Medullary centers consisting of

1. Dorsal respiratory group of neurons
2. Ventral respiratory group of neurons

B. Pontine centers

3. Apneustic center
4. Pneumotaxic center.



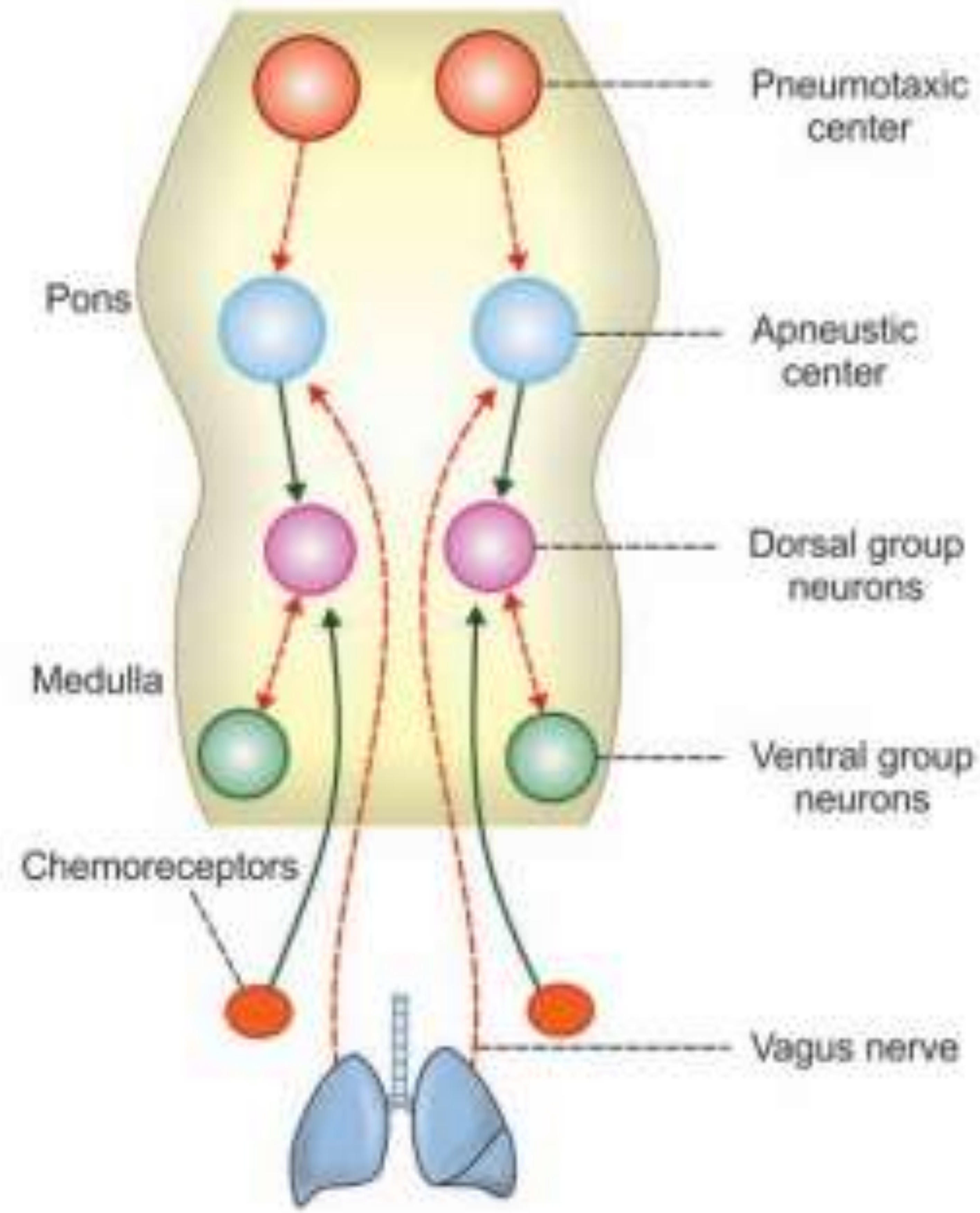
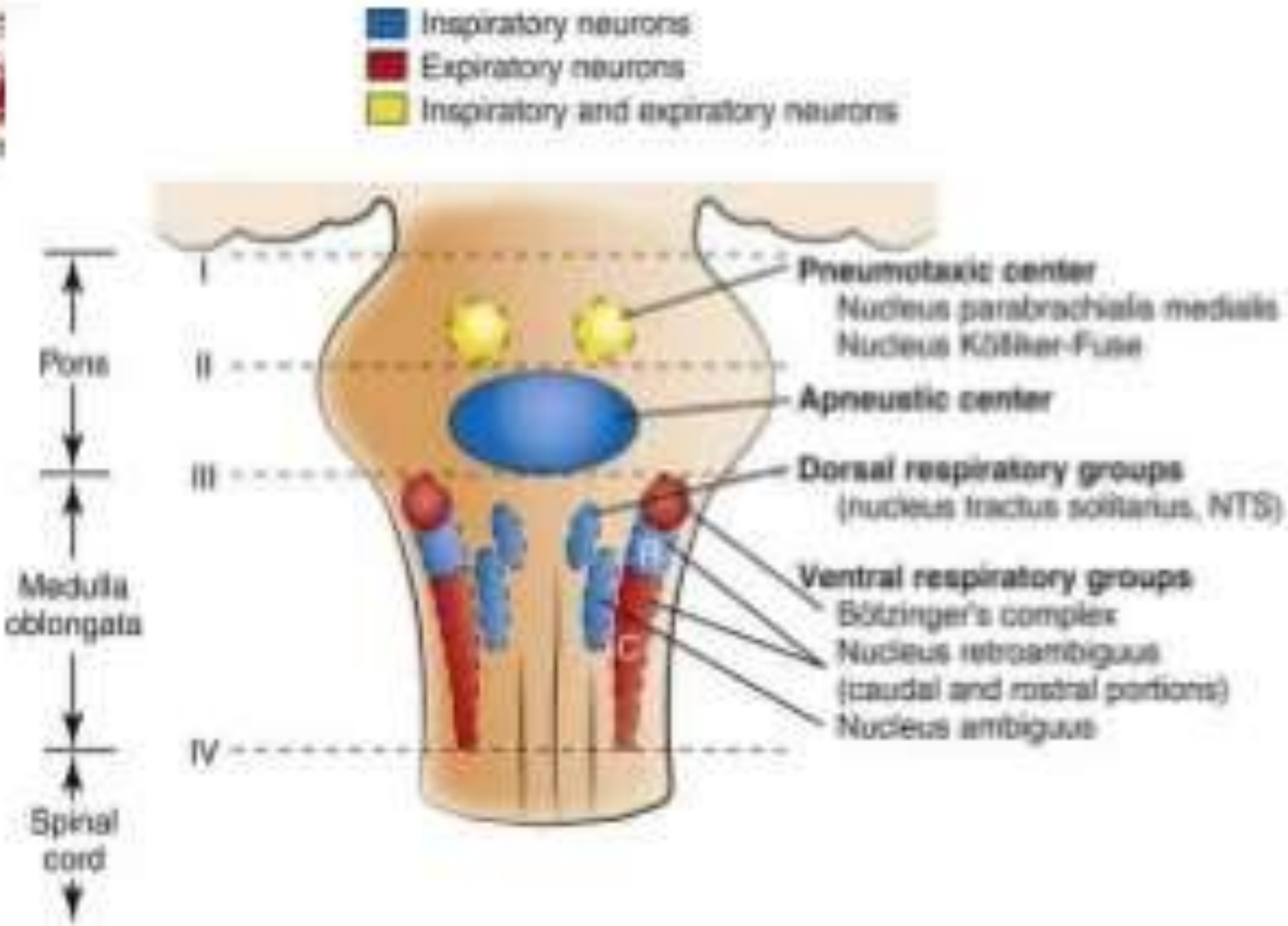
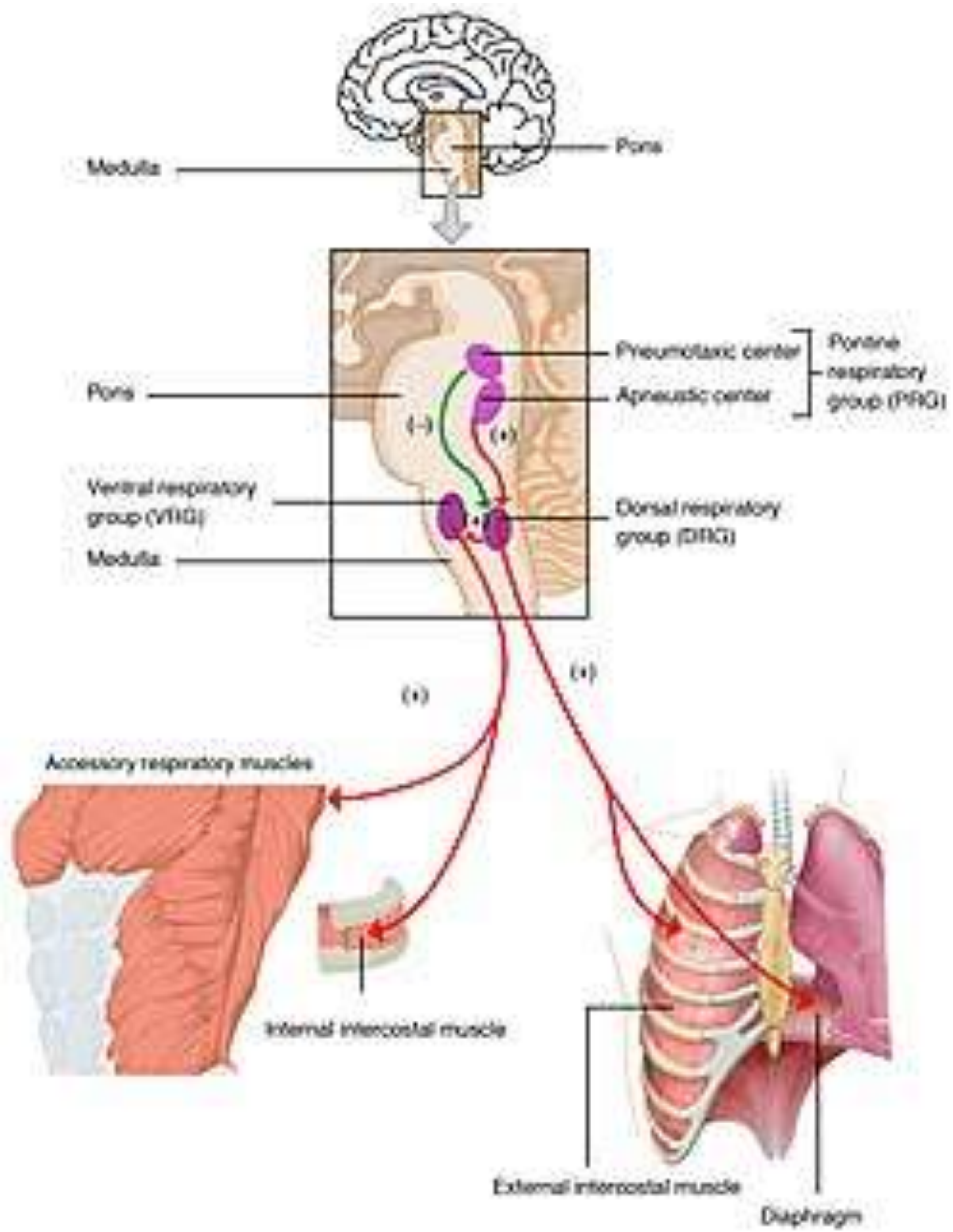
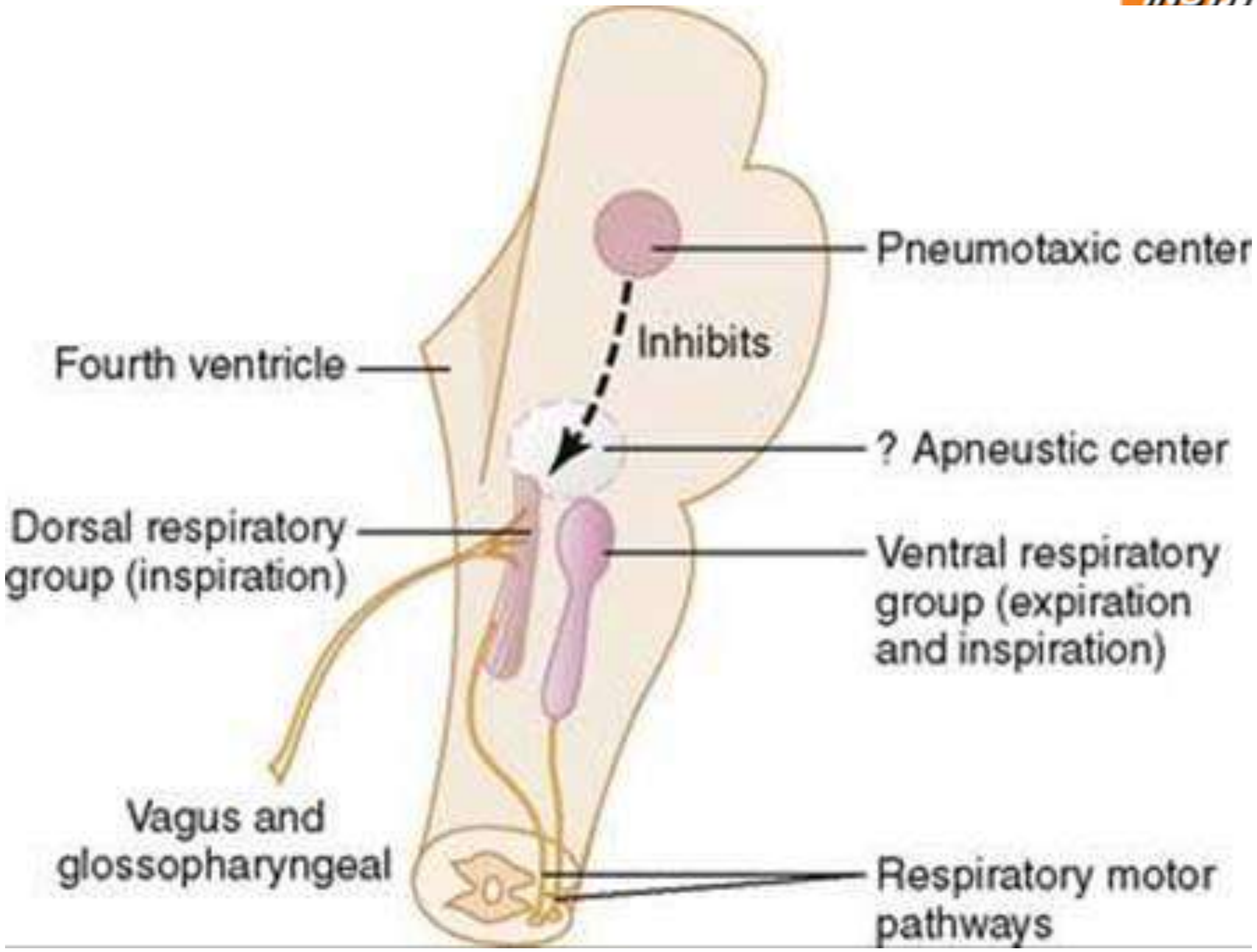


FIGURE 126.1: Nervous regulation of respiration.
Solid green line = Stimulation. Dotted red line = Inhibition.




Pons
Medulla
Pneumotaxic center
Apneustic center
Pontine respiratory group (PRG)
Pons
(-)
(+)
Ventral respiratory group (VRG)
Dorsal respiratory group (DRG)
Medulla
(+)
(+)
Accessory respiratory muscles
Internal intercostal muscle
External intercostal muscle
Diaphragm


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

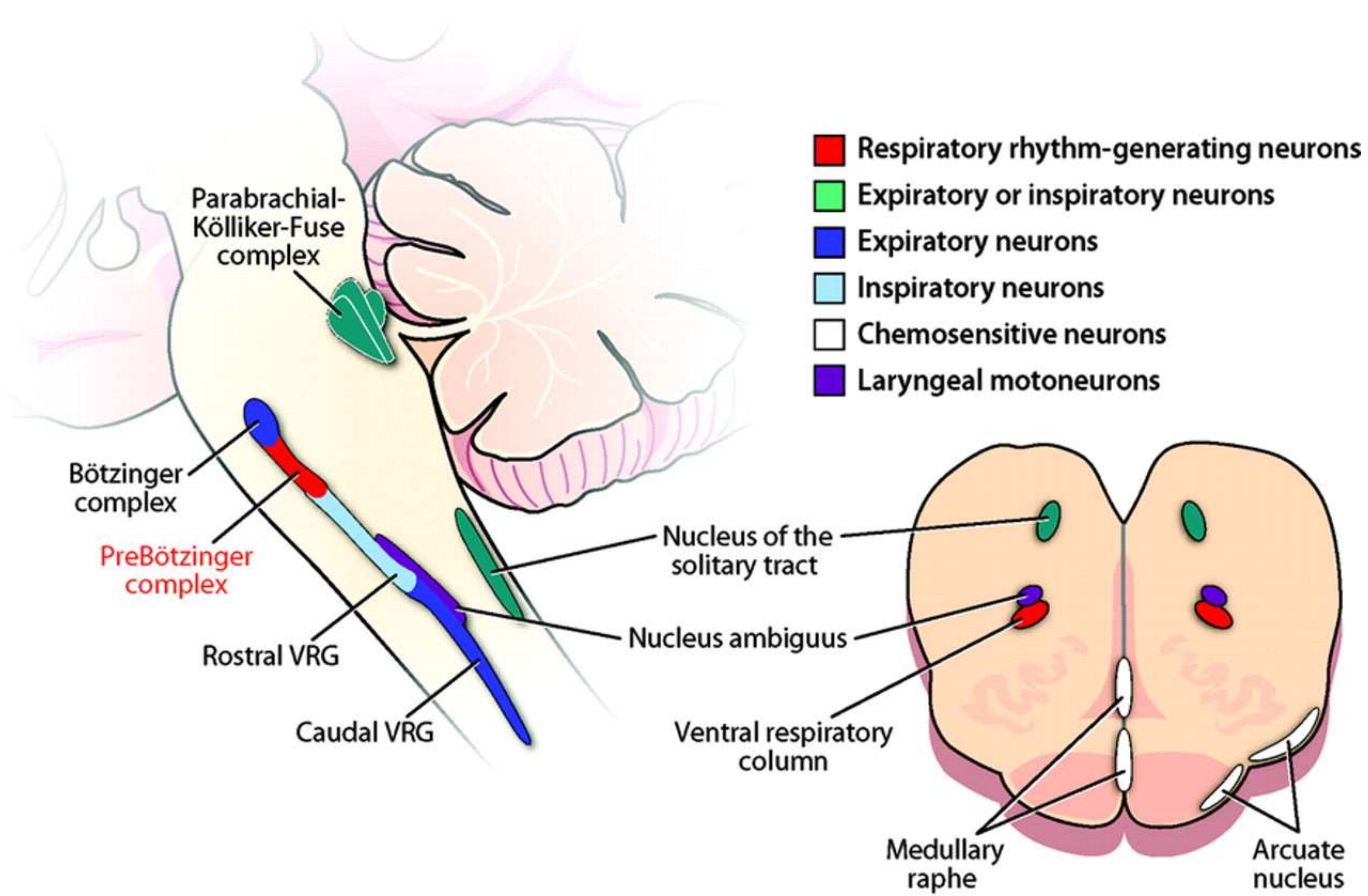
MEDULLARY CENTERS

1. Dorsal Respiratory Group of Neurons

Situation

Dorsal respiratory group of neurons are diffusely situated in the **nucleus of tractus solitarius** which is present in the upper part of the **medulla oblongata**.

Usually, these neurons are collectively called **inspiratory center.**


Respiratory rhythm-generating neurons
Expiratory or inspiratory neurons
Expiratory neurons
Inspiratory neurons
Chemosensitive neurons
Laryngeal motoneurons
Parabrachial-Kölliker-Fuse complex
Bötzinger complex
PreBötzinger complex
Rostral VRG
Caudal VRG
Nucleus of the solitary tract
Nucleus ambiguus
Ventral respiratory column
Medullary raphe
Arcuate nucleus

All the neurons of **dorsal respiratory group are inspiratory neurons** and generate inspiratory ramp by the virtue of their auto rhythmic property.

FUNCTION

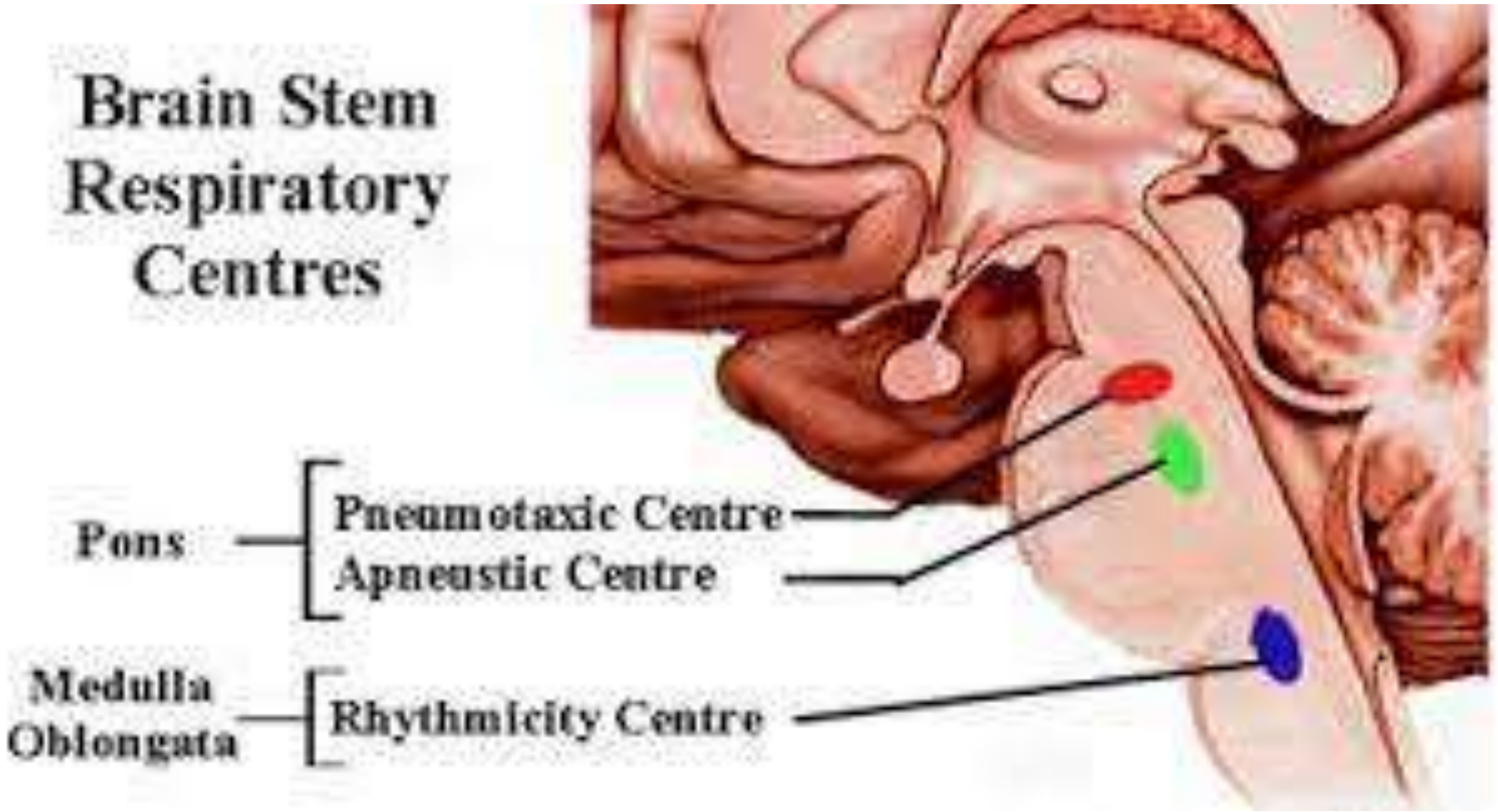
Dorsal group of neurons are responsible for **basic rhythm of respiration .**

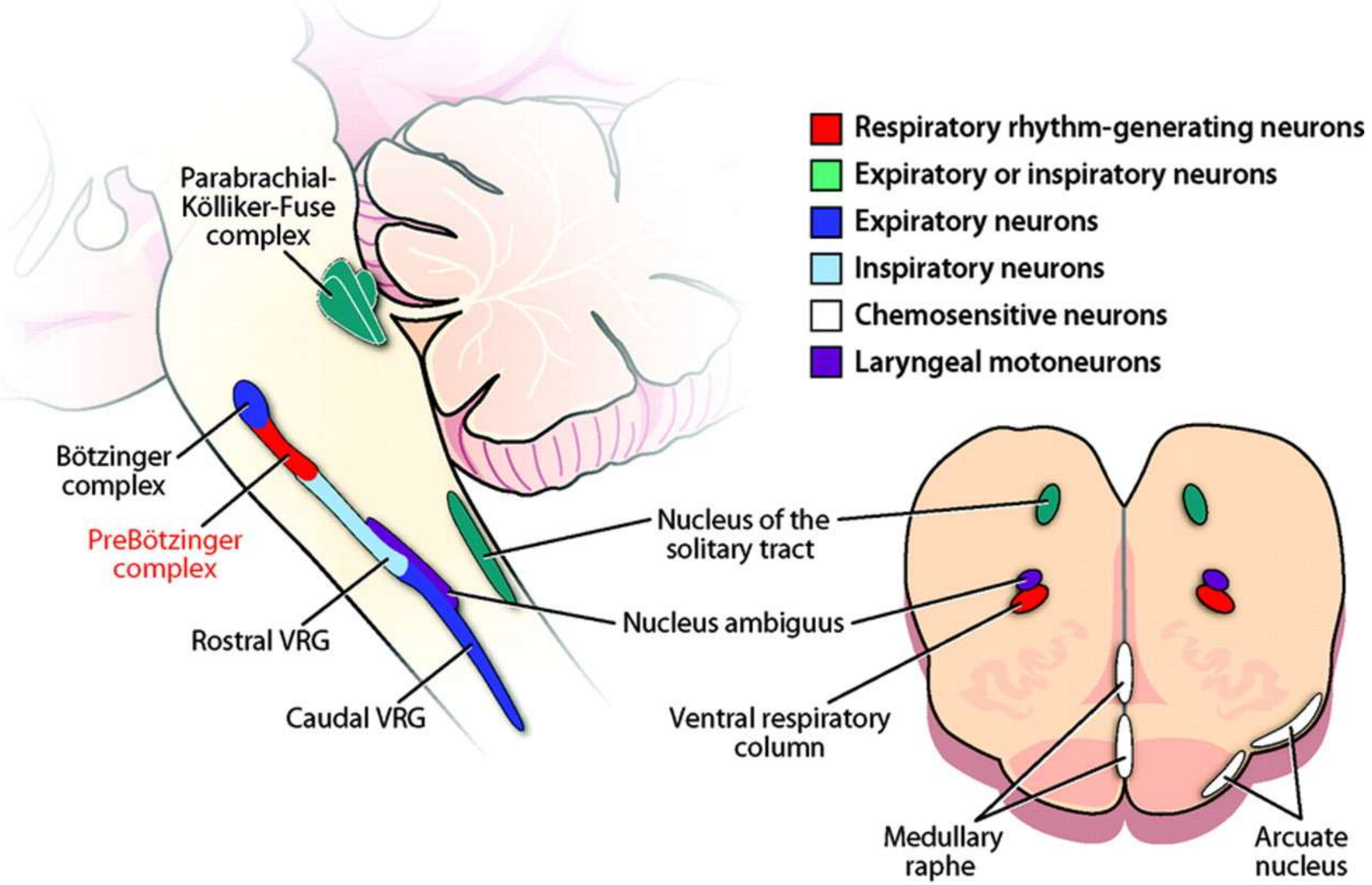
Experimental evidence

Electrical stimulation of these neurons in animals by using needle electrode causes contraction of inspiratory muscles and prolonged inspiration.

TABLE 126.1: Medullary centers

Features	Dorsal group	Ventral group
Situation	Diffusely situated in nucleus of tractus solitarius	In nucleus ambiguous and nucleus retroambiguous
Type of neurons	Inspiratory neurons	Inspiratory and expiratory neurons
Function	Always active Generate inspiratory ramp Has autorhythmic property	Inactive during quiet breathing Active during forced breathing





2. Ventral Respiratory Group of Neurons

Situation

Ventral respiratory group of neurons are present in nucleus ambiguous and nucleus retro ambiguous.

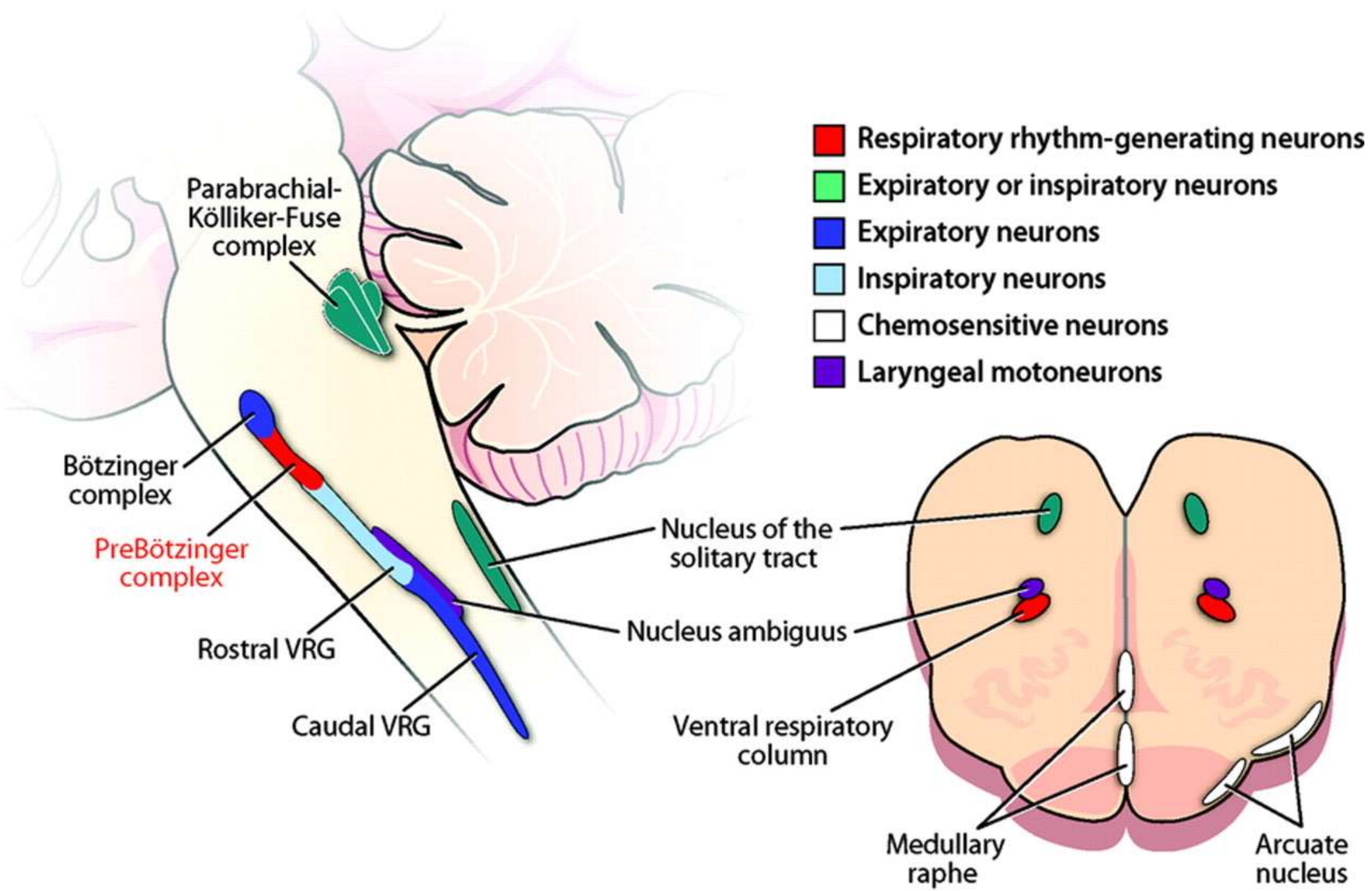
These two nuclei are situated in the medulla oblongata, anterior and lateral to the nucleus of tractus solitarius.

Earlier, the **ventral group neurons were collectively called expiratory** center.

Ventral respiratory group has both inspiratory and expiratory neurons.

Inspiratory neurons are found in the central area of the group.

Expiratory neurons are in the caudal and rostral areas of the group


Respiratory rhythm-generating neurons
Expiratory or inspiratory neurons
Expiratory neurons
Inspiratory neurons
Chemosensitive neurons
Laryngeal motoneurons
Parabrachial-Kölliker-Fuse complex
Bötzinger complex
PreBötzinger complex
Rostral VRG
Caudal VRG
Nucleus of the solitary tract
Nucleus ambiguus
Ventral respiratory column
Medullary raphe
Arcuate nucleus

FUNCTION

Normally, ventral group neurons are **inactive during quiet breathing and become active during forced breathing.**

During forced breathing, these **neurons stimulate** both **inspiratory muscles and expiratory muscles.**

Experimental evidence

Electrical stimulation of the **inspiratory neurons** in ventral group causes contraction of inspiratory muscles and prolonged inspiration.

Stimulation of **expiratory neurons** causes contraction of expiratory muscles and prolonged expiration.

PONTINE CENTERS

3. Apneustic Center

Situation

Apneustic center is situated in the reticular formation of lower pons.

Function

Apneustic center increases depth of inspiration by acting directly on dorsal group neurons

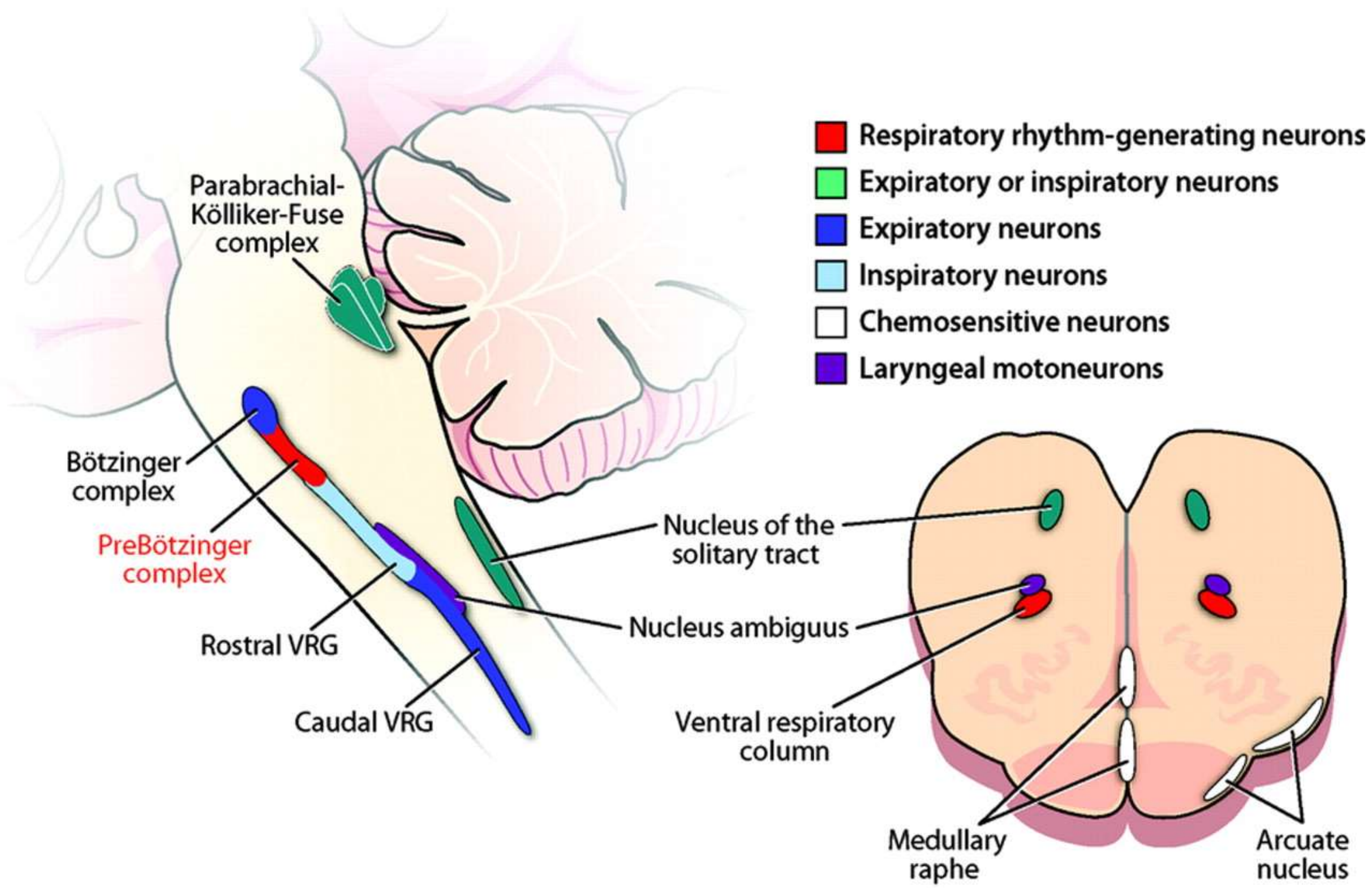
4. PNEUMOTAXIC CENTER

Situation

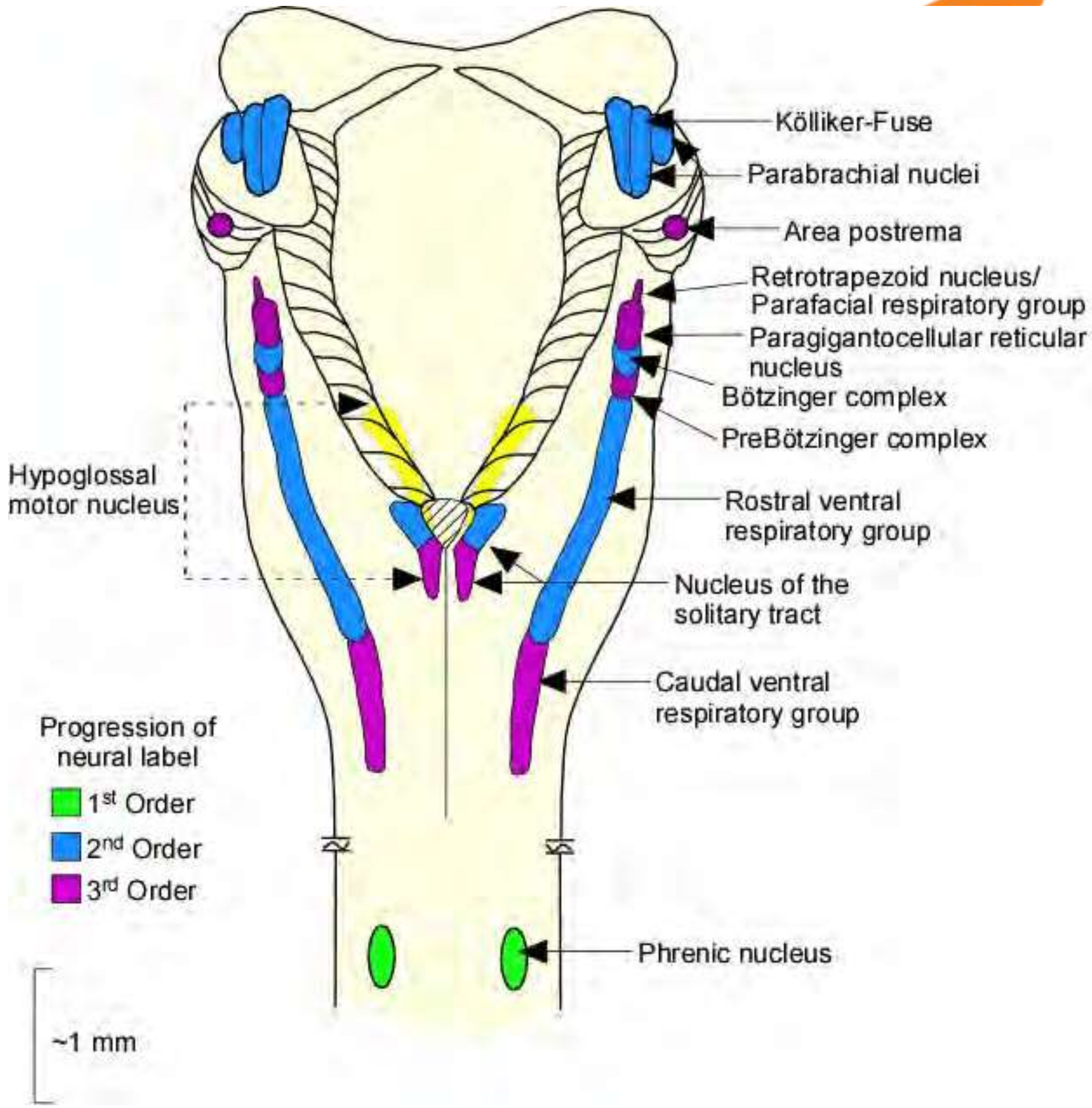
Pneumotaxic center is situated in the dorsolateral part of reticular formation in upper pons.

It is formed by neurons of **medial parabrachial and subparabrachial nuclei.**

Subparabrachial nucleus is also called ventral parabrachial or Kölliker-Fuse nucleus.



Respiratory rhythm-generating neurons
Expiratory or inspiratory neurons
Expiratory neurons
Inspiratory neurons
Chemosensitive neurons
Laryngeal motoneurons
Parabrachial-Kölliker-Fuse complex
Bötzinger complex
PreBötzinger complex
Rostral VRG
Caudal VRG
Nucleus of the solitary tract
Nucleus ambiguus
Ventral respiratory column
Medullary raphe
Arcuate nucleus



Kölliker-Fuse
Parabrachial nuclei
Area postrema
Retrotrapezoid nucleus/ Parafacial respiratory group
Paragigantocellular reticular nucleus
Bötzinger complex
PreBötzinger complex
Rostral ventral respiratory group
Hypoglossal motor nucleus
Nucleus of the solitary tract
Caudal ventral respiratory group
Progression of neural label
1st Order
2nd Order
3rd Order
Phrenic nucleus
~1 mm

FUNCTION

Primary function of pneumotaxic center is to **control the medullary respiratory centers, particularly the dorsal group neurons.**

It acts through apneustic center.

Pneumotaxic center inhibits the apneustic center so that the dorsal group neurons are inhibited.

Because of this, inspiration stops and expiration starts.

Thus, pneumotaxic center influences the switching between inspiration and expiration.

Pneumotaxic center increases respiratory rate by reducing the duration of inspiration.

CONNECTIONS OF RESPIRATORY CENTERS

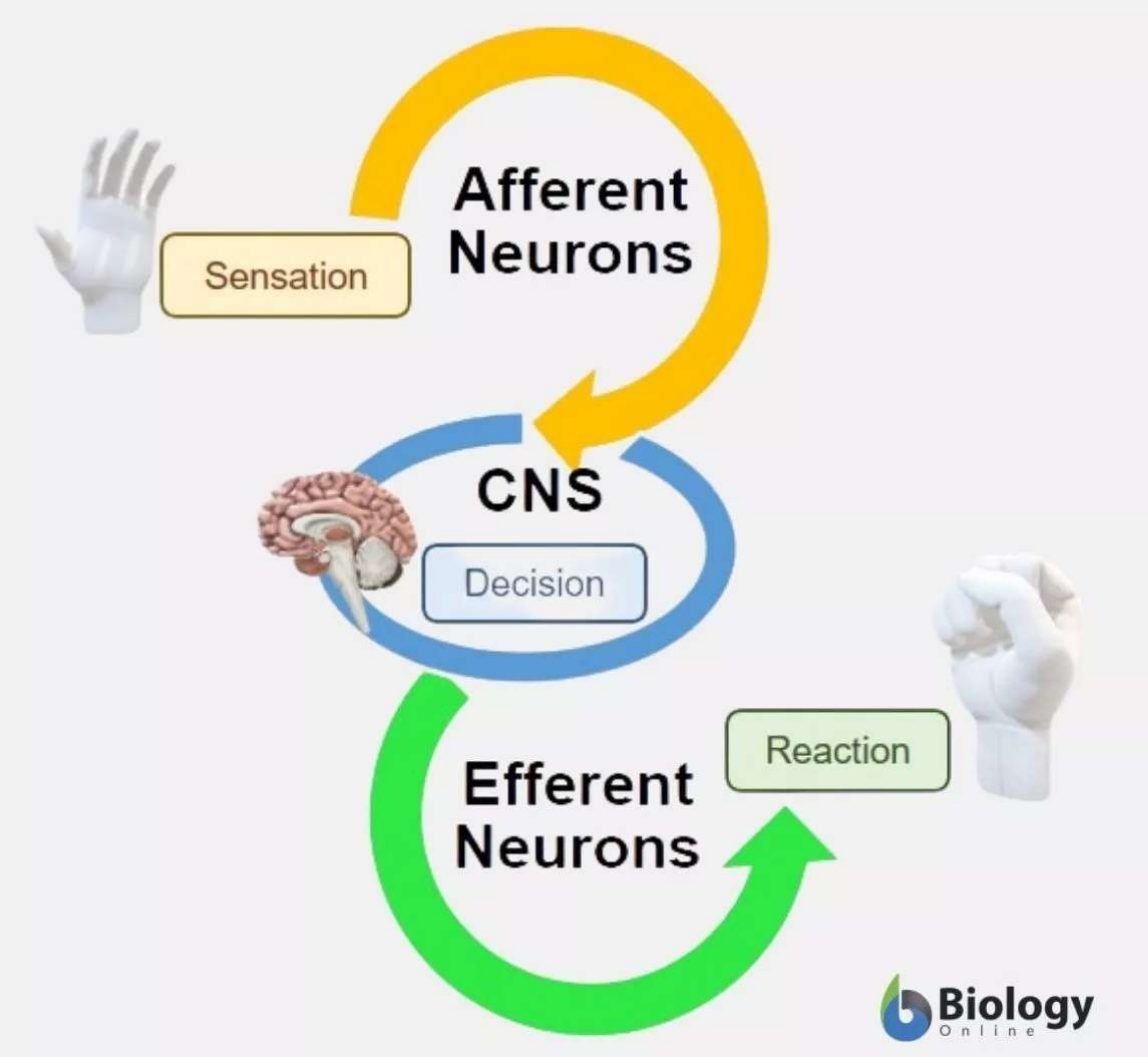
Efferent Pathway

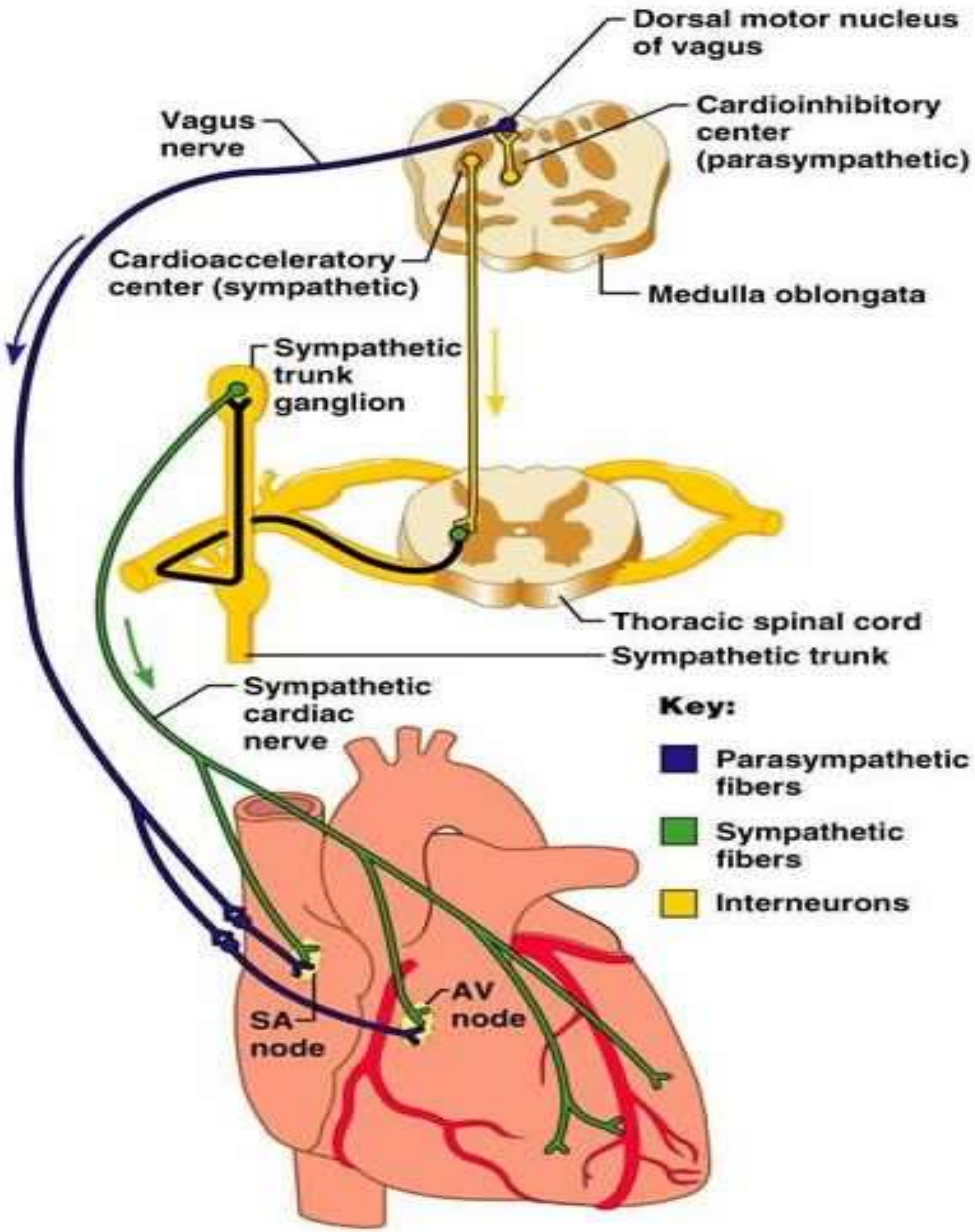
Nerve fibers from respiratory centers leave the brainstem and descend in anterior part of lateral columns of spinal cord.

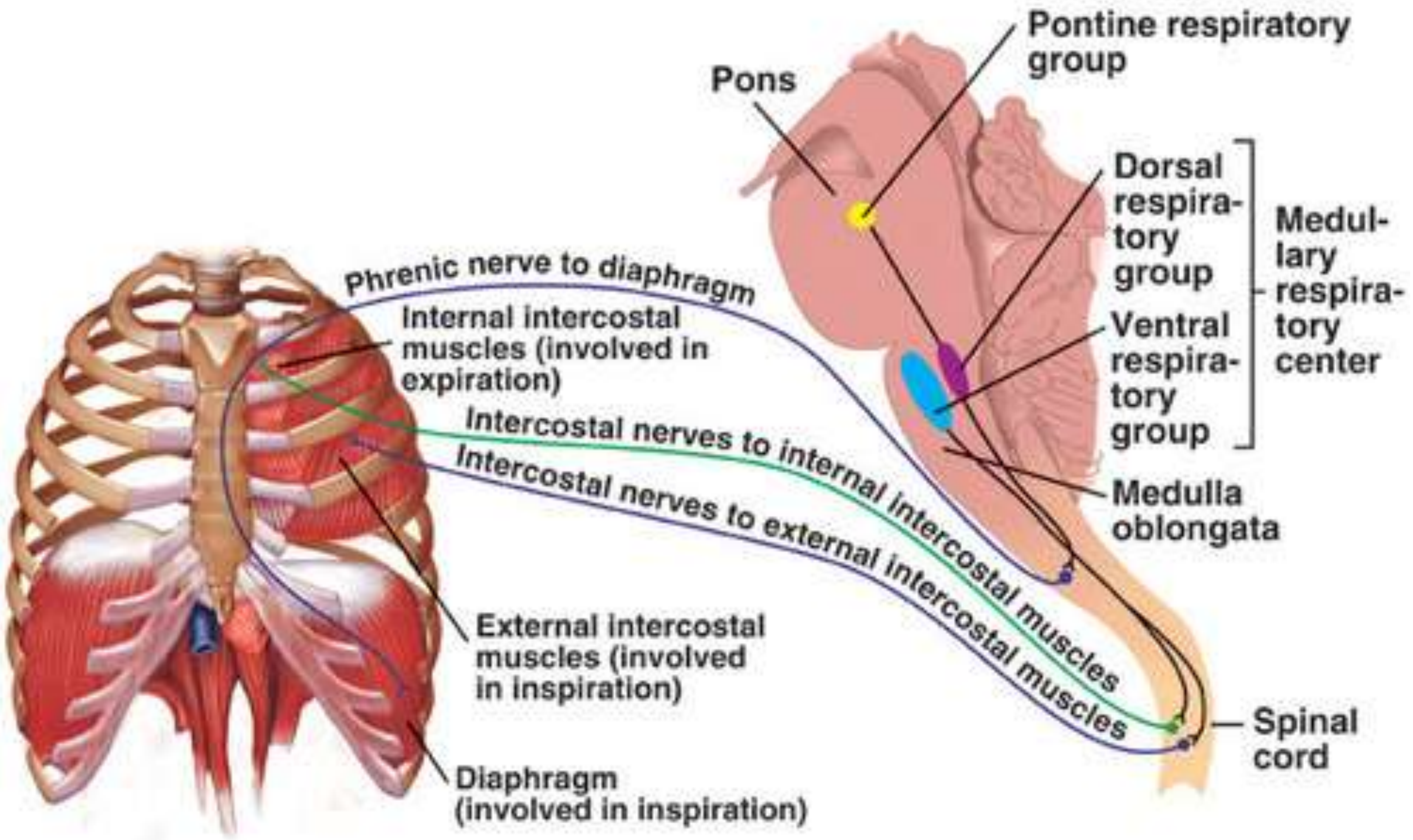
These nerve fibers terminate on motor neurons in the anterior horn cells of cervical and thoracic segments of spinal cord.

From motor neurons of spinal cord, two sets of nerve fibers arise:

1. **Phrenic nerve fibers** (C3 to C5), which supply the diaphragm
2. **Intercostal nerve fibers** (T1 to T11), which supply the external intercostal muscles. **Vagus nerve** also contains some efferent fibers from the respiratory centers


Afferent Neurons
Sensation
CNS
Decision
Efferent Neurons
Reaction
Biology Online


Dorsal motor nucleus of vagus
Vagus nerve
Cardioinhibitory center (parasympathetic)
Cardioacceleratory center (sympathetic)
Medulla oblongata
Sympathetic trunk ganglion
Thoracic spinal cord
Sympathetic trunk
Sympathetic cardiac nerve
Key:
Parasympathetic fibers
Sympathetic fibers
Interneurons
SA node
AV node

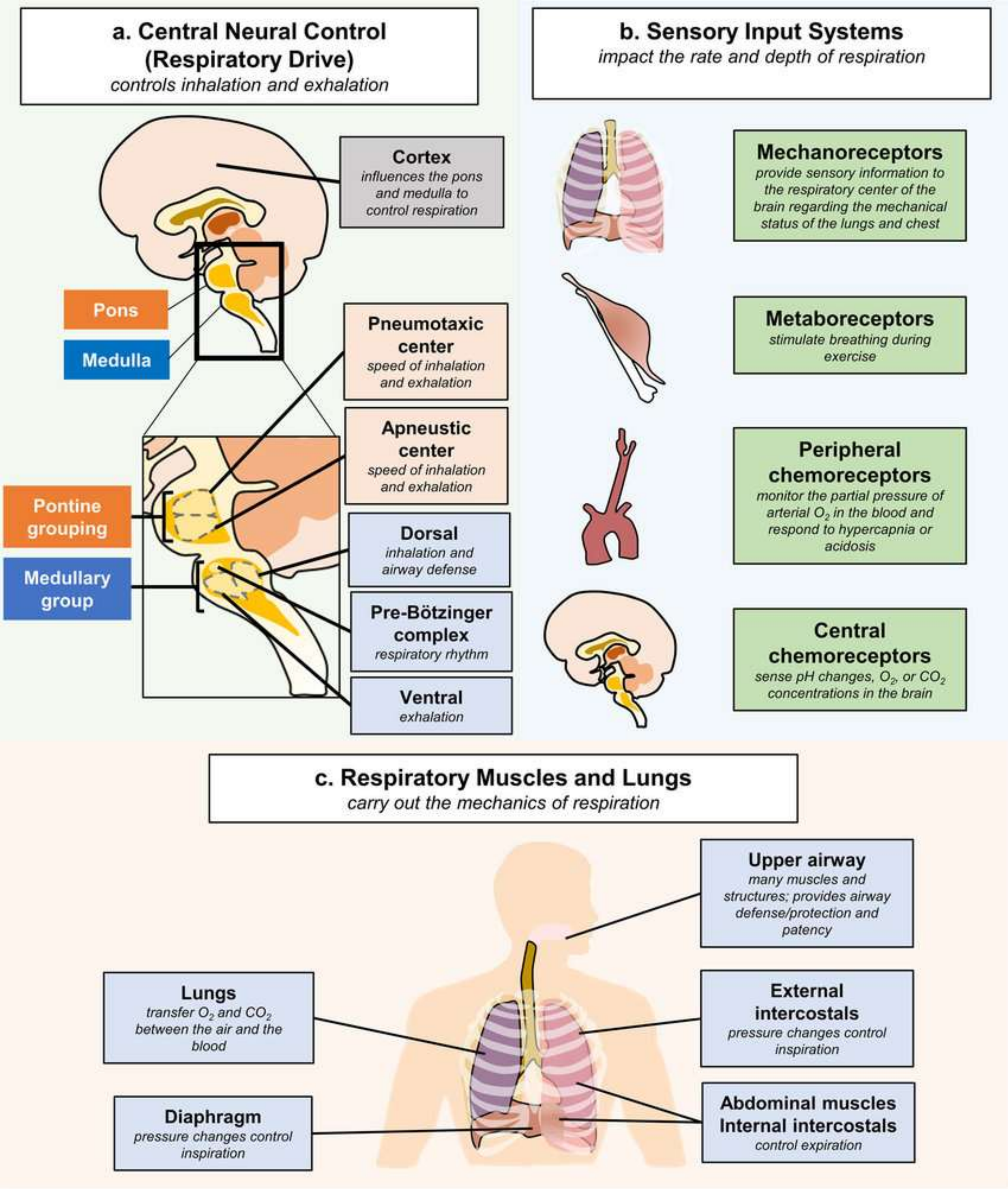

Pontine respiratory group
Pons
Dorsal respiratory group
Medullary respiratory center
Ventral respiratory group
Medulla oblongata
Phrenic nerve to diaphragm
Internal intercostal muscles (involved in expiration)
Intercostal nerves to internal intercostal muscles
Intercostal nerves to external intercostal muscles
External intercostal muscles (involved in inspiration)
Diaphragm (involved in inspiration)
Spinal cord

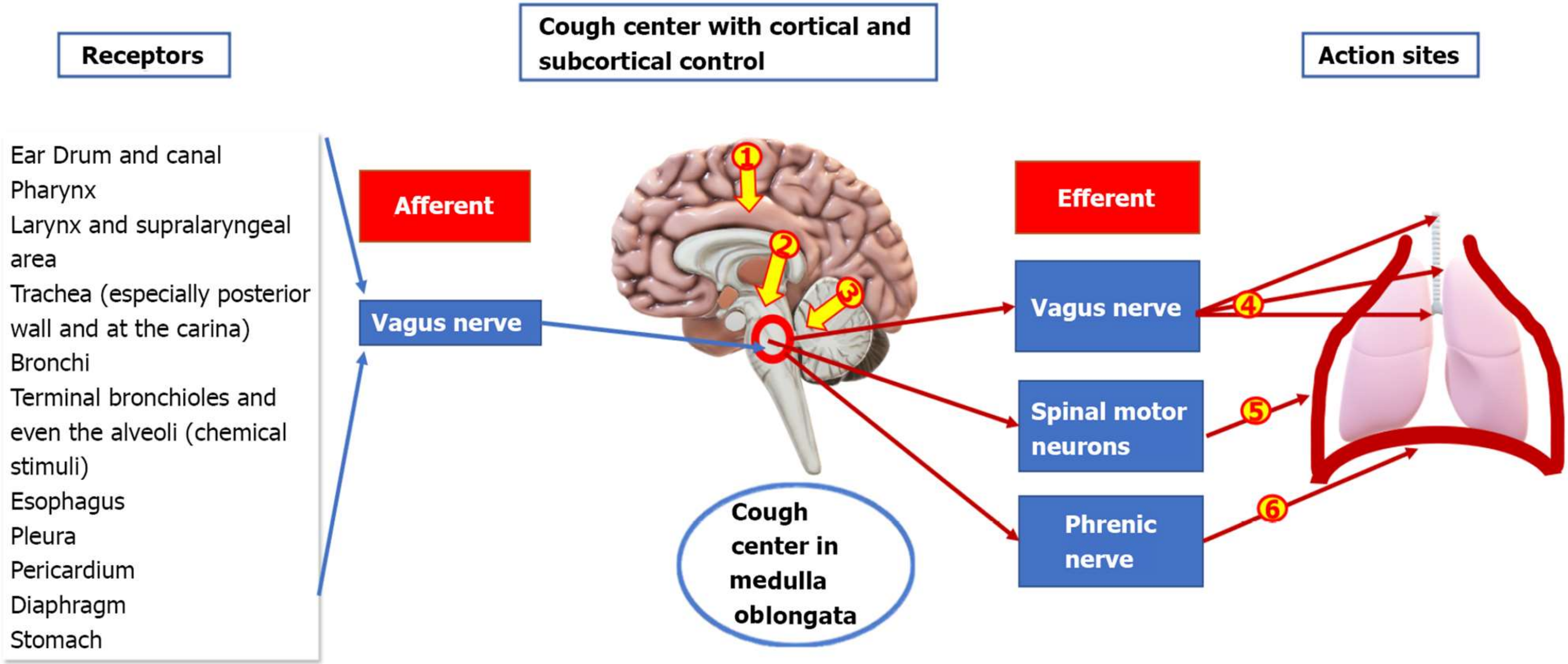
Afferent Pathway

Respiratory centers receive afferent impulses from:

1. **Peripheral chemoreceptors and baroreceptors** via branches of glossopharyngeal and vagus nerves.

2. Stretch receptors of lungs via vagus nerve. By receiving afferent impulses from these receptors, respiratory centers modulate the movements of thoracic cage and lungs through efferent nerve fibers


a. Central Neural Control (Respiratory Drive)
controls inhalation and exhalation
Cortex
influences the pons and medulla to control respiration
Pons
Medulla
Pneumotaxic center
speed of inhalation and exhalation
Apneustic center
speed of inhalation and exhalation
Pontine grouping
Medullary group
Dorsal
inhalation and airway defense
Pre-Bötzinger complex
respiratory rhythm
Ventral
exhalation
b. Sensory Input Systems
impact the rate and depth of respiration
Mechanoreceptors
provide sensory information to the respiratory center of the brain regarding the mechanical status of the lungs and chest
Metaboreceptors
stimulate breathing during exercise
Peripheral chemoreceptors
monitor the partial pressure of arterial O_2 in the blood and respond to hypercapnia or acidosis
Central chemoreceptors
sense pH changes, O_2, or CO_2 concentrations in the brain
c. Respiratory Muscles and Lungs
carry out the mechanics of respiration
Upper airway
many muscles and structures; provides airway defense/protection and patency
Lungs
transfer O_2 and CO_2 between the air and the blood
External intercostals
pressure changes control inspiration
Diaphragm
pressure changes control inspiration
Abdominal muscles
Internal intercostals
control expiration



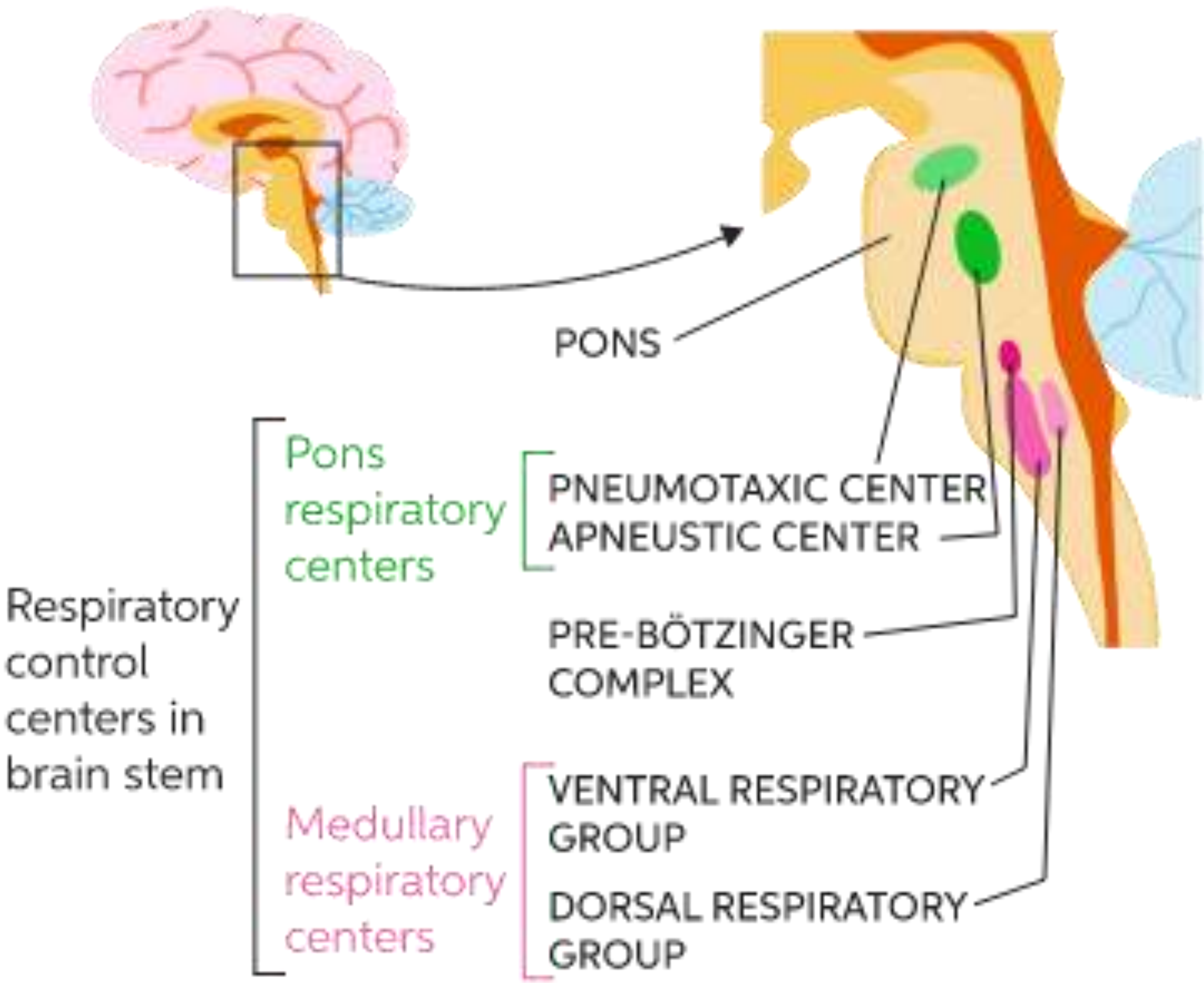
DOI: 10.5492/wjccm.v11.i3.115

ROLE OF PONTINE CENTERS

Pontine respiratory centers regulate the medullary centers.

Apneustic center accelerates the activity of dorsal group of neurons and the stimulation of this center causes **prolonged inspiration.**

Pneumotaxic center inhibits the apneustic center and restricts the duration of inspiration.


PONS
Respiratory control centers in brain stem
Pons respiratory centers
PNEUMOTAXIC CENTER
APNEUSTIC CENTER
PRE-BÖTZINGER COMPLEX
Medullary respiratory centers
VENTRAL RESPIRATORY GROUP
DORSAL RESPIRATORY GROUP

PRE-BÖTZINGER COMPLEX

Pre-Bötzinger complex (pre-BötC) is an additional respiratory center found in **animals**.

It is formed by a group of neurons called pacemaker neurons, located in the ventrolateral part of medulla.

Pacemaker neurons generate the **rhythmic respiratory impulses**.

Medullary centers send nerve fibers into this complex. Exact functioning mechanism of this complex is not known.

FACTORS AFFECTING RESPIRATORY CENTERS

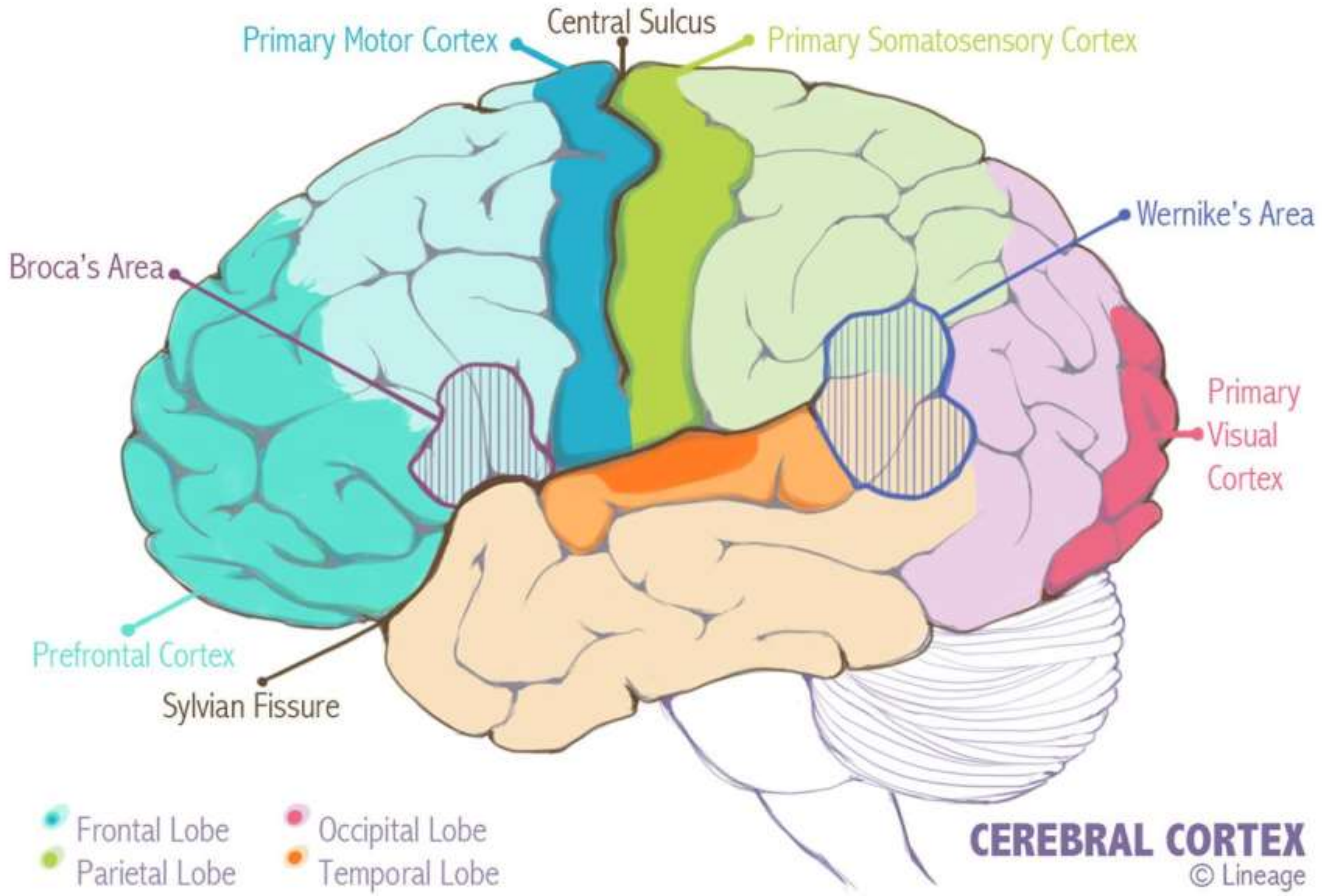
Respiratory centers regulate the respiratory movements by receiving impulses from various sources in the body.

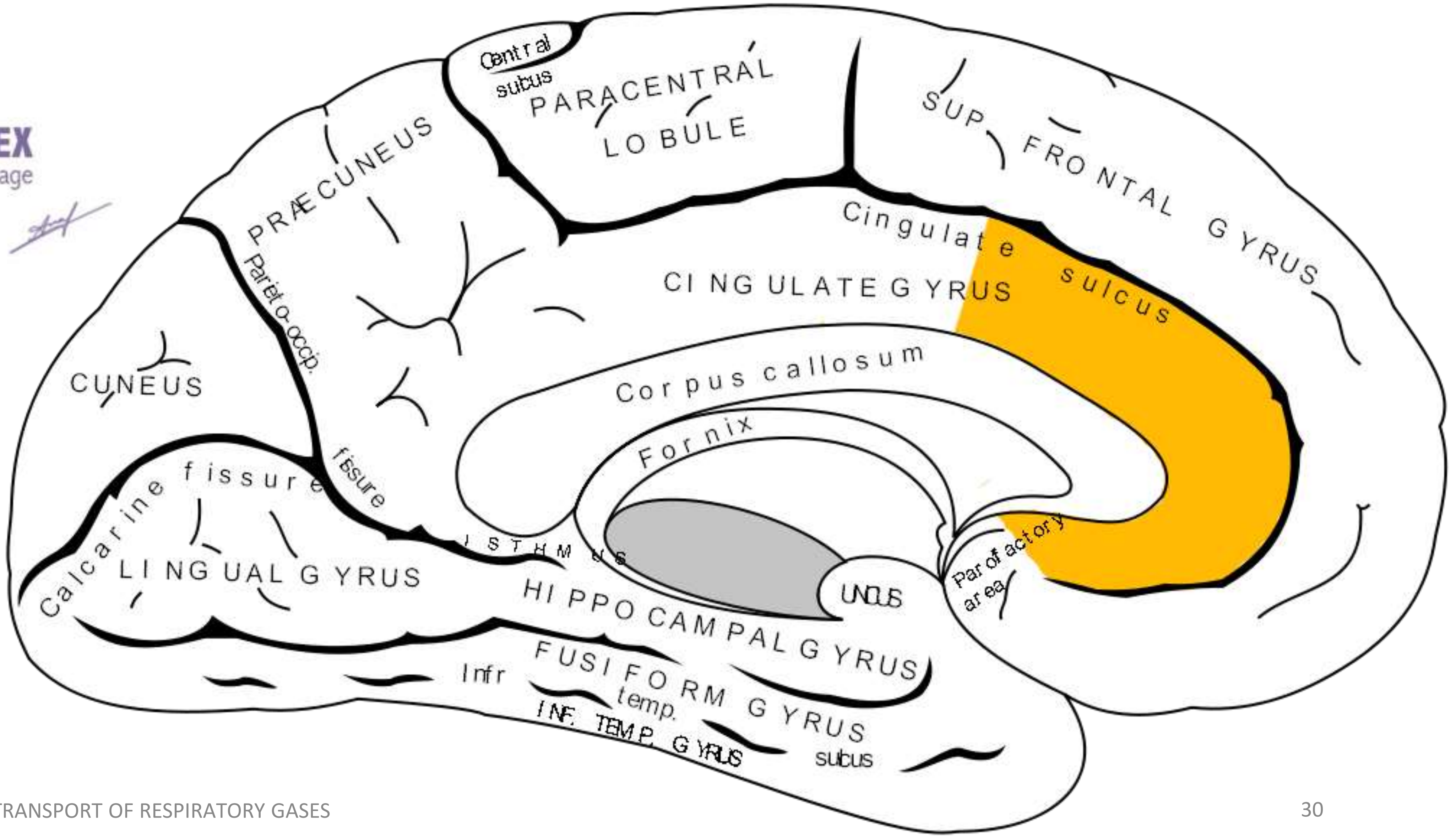
1. Impulses from Higher Centers

Higher centers alter the respiration by sending impulses directly to dorsal group of neurons.

Impulses from anterior cingulate gyrus, genu of corpus callosum, olfactory tubercle and posterior orbital gyrus of cerebral cortex inhibit respiration.

Impulses from motor area and Sylvian area of cerebral cortex cause forced breathing.


Primary Motor Cortex
Central Sulcus
Primary Somatosensory Cortex
Wernike's Area
Broca's Area
Primary
Visual
Cortex
Prefrontal Cortex
Sylvian Fissure
Frontal Lobe
Parietal Lobe
Occipital Lobe
Temporal Lobe
CEREBRAL CORTEX
© Lineage


Central sulcus
PARACENTRAL
LOBULE
SUP. FRONTAL GYRUS
PRÆCUNEUS
Cingulate sulcus
CINGULATE GYRUS
Parieto-occip.
fissure
CUNEUS
Corpus callosum
Fornix
Calcarine fissure
LINGUAL GYRUS
ISTHMUS
HIPPOCAMPAL GYRUS
UNCUS
Parolfactory area
FUSIFORM GYRUS
Infr. temp. sulcus
INF. TEMP. GYRUS

2. IMPULSES FROM STRETCH RECEPTORS OF LUNGS: HERING-BREUER REFLEX

Hering-Breuer reflex is a protective reflex that restricts inspiration and prevents overstretching of lung tissues.

It is initiated by the stimulation of stretch receptors of air passage.

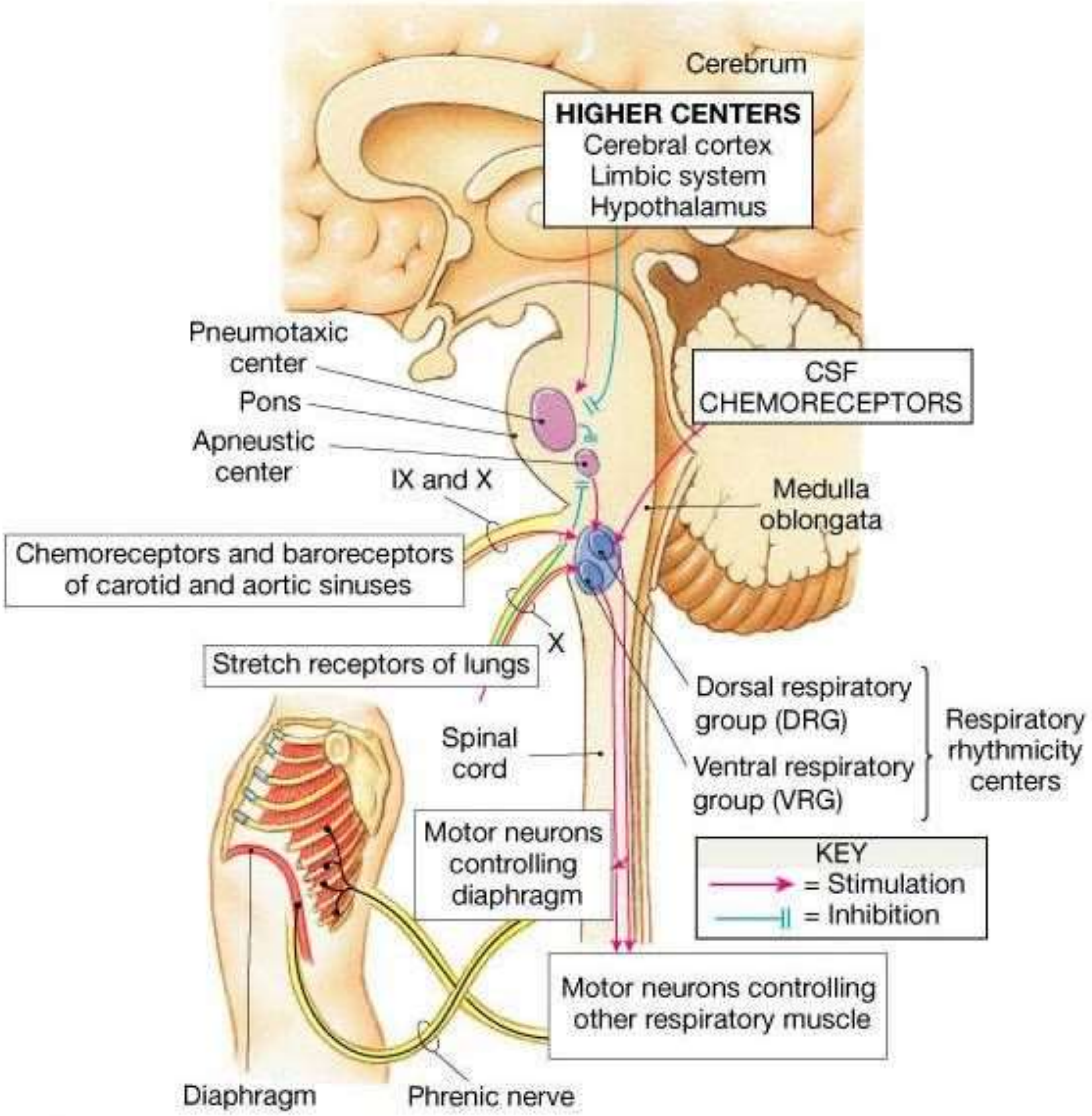
Stretch receptors are the receptors which give response to stretch of the tissues.

These receptors are situated on the wall of the bronchi and bronchioles.

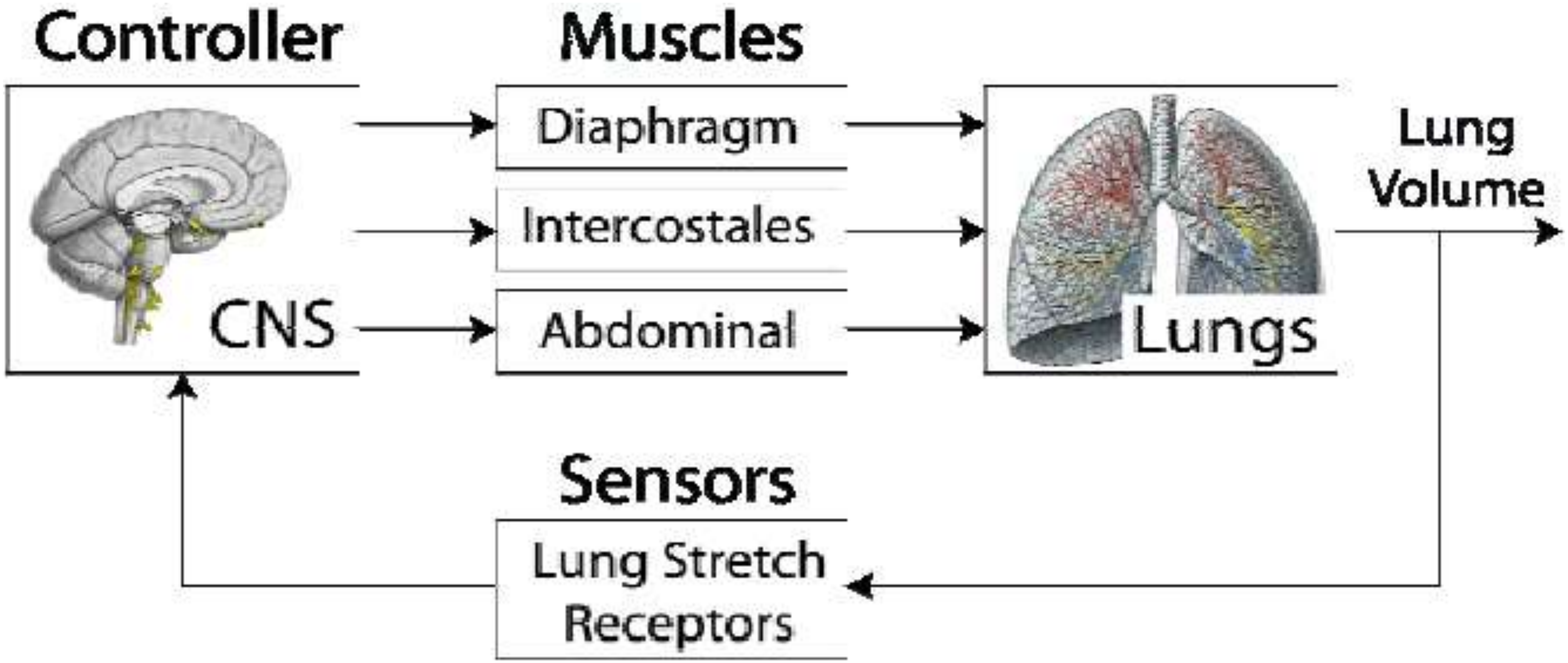
Expansion of lungs during inspiration stimulates the stretch receptors.

Impulses from stretch receptors reach the dorsal group neurons via vagal afferent fibers and inhibit them.

So, inspiration stops and expiration starts.Thus, the overstretching of lung tissues is prevented.



Cerebrum
HIGHER CENTERS
Cerebral cortex
Limbic system
Hypothalamus
Pneumotaxic center
Pons
Apneustic center
IX and X
CSF CHEMORECEPTORS
Medulla oblongata
Chemoreceptors and baroreceptors of carotid and aortic sinuses
X
Stretch receptors of lungs
Dorsal respiratory group (DRG)
Ventral respiratory group (VRG)
Respiratory rhythmicity centers
Spinal cord
Motor neurons controlling diaphragm
KEY
= Stimulation
= Inhibition
Motor neurons controlling other respiratory muscle
Diaphragm
Phrenic nerve


Controller
Muscles
Diaphragm
Intercostales
Abdominal
CNS
Lungs
Lung
Volume
Sensors
Lung Stretch
Receptors

However, Hering-Breuer reflex does not operate during quiet breathing.

It operates, only when the **tidal volume increases beyond 1,000 mL**. Hering-Breuer inflation reflex and deflation reflex

The above mentioned reflex is called Hering-Breuer inflation reflex since it restricts the inspiration and limits the overstretching of lung tissues.

Reverse of this reflex is called **Hering-Breuer deflation reflex** and it takes place during expiration.
During expiration, as the stretching of lungs is absent, deflation occurs.

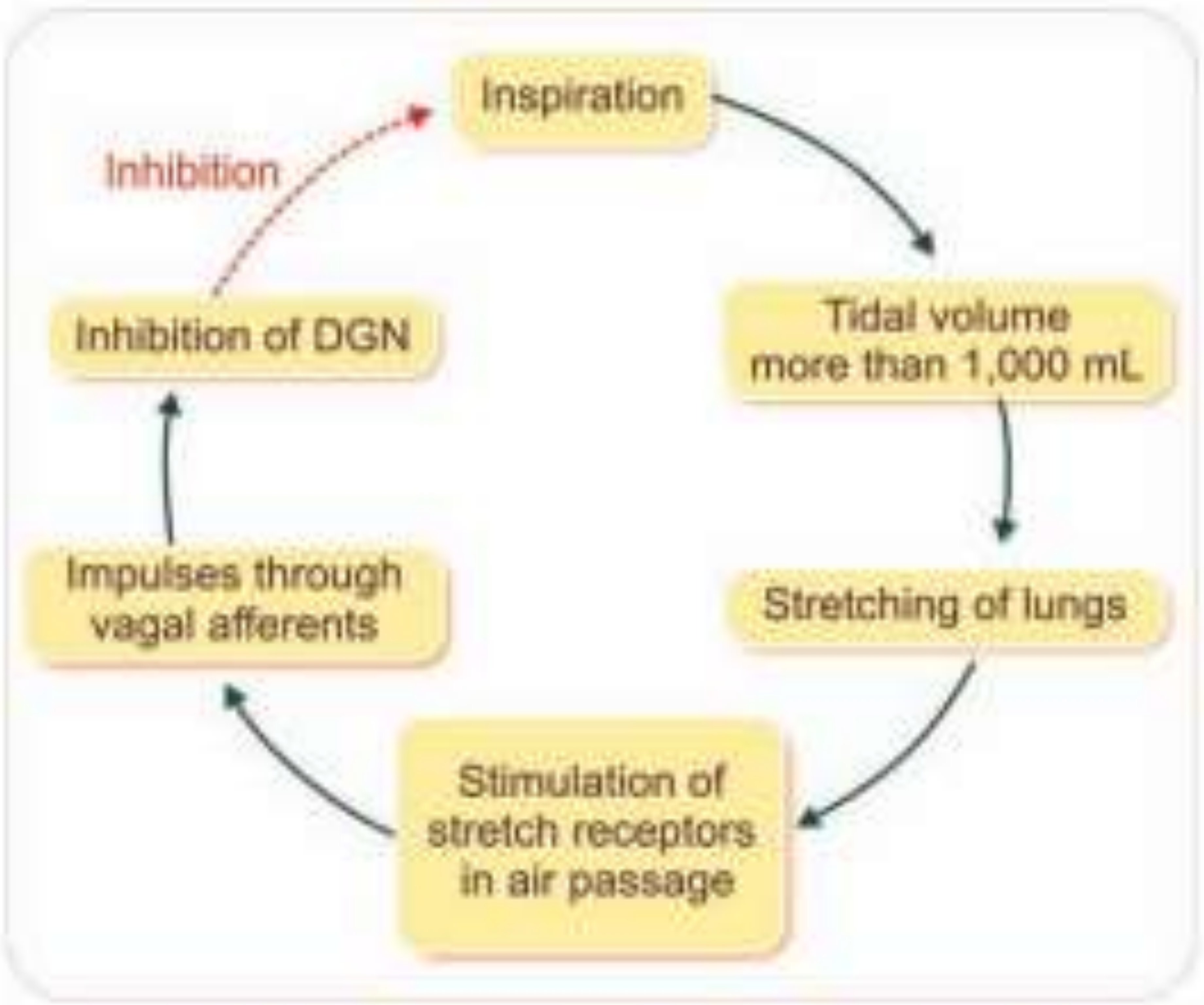


FIGURE 126.2: Hering-Breuer inflation reflex. DGN = Dorsal respiratory group of neurons. Dashed red arrow indicates inhibition.

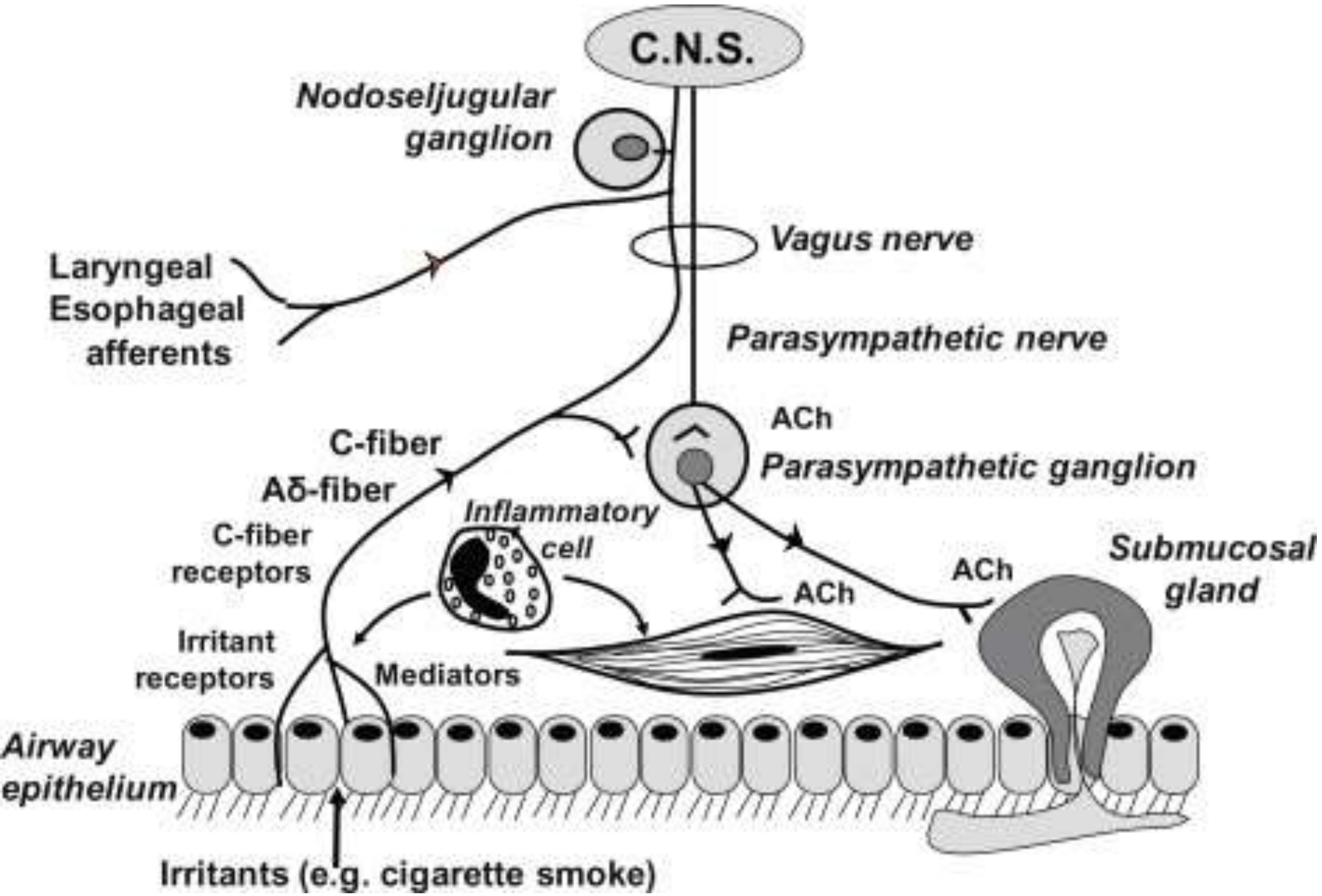
3. IMPULSES FROM ‘J’ RECEPTORS OF LUNGS

‘J’ receptors are **juxtacapillary receptors** which are present on the wall of the alveoli and have close contact with the pulmonary capillaries.

AS Paintal discovered that these receptors are the **sensory nerve endings of vagus.**

Nerve fibers from these receptors are non-myelinated and belong to C type.

Few receptors are found on the **wall of the bronchi.**


C.N.S.
Nodoseljugular
ganglion
Vagus nerve
Laryngeal
Esophageal
afferents
Parasympathetic nerve
ACh
Parasympathetic ganglion
C-fiber
Aδ-fiber
Inflammatory
cell
C-fiber
receptors
ACh
ACh
Submucosal
gland
Irritant
receptors
Mediators
Airway
epithelium
Irritants (e.g. cigarette smoke)

Conditions when ‘J’ receptors are stimulated

i. Pulmonary congestion

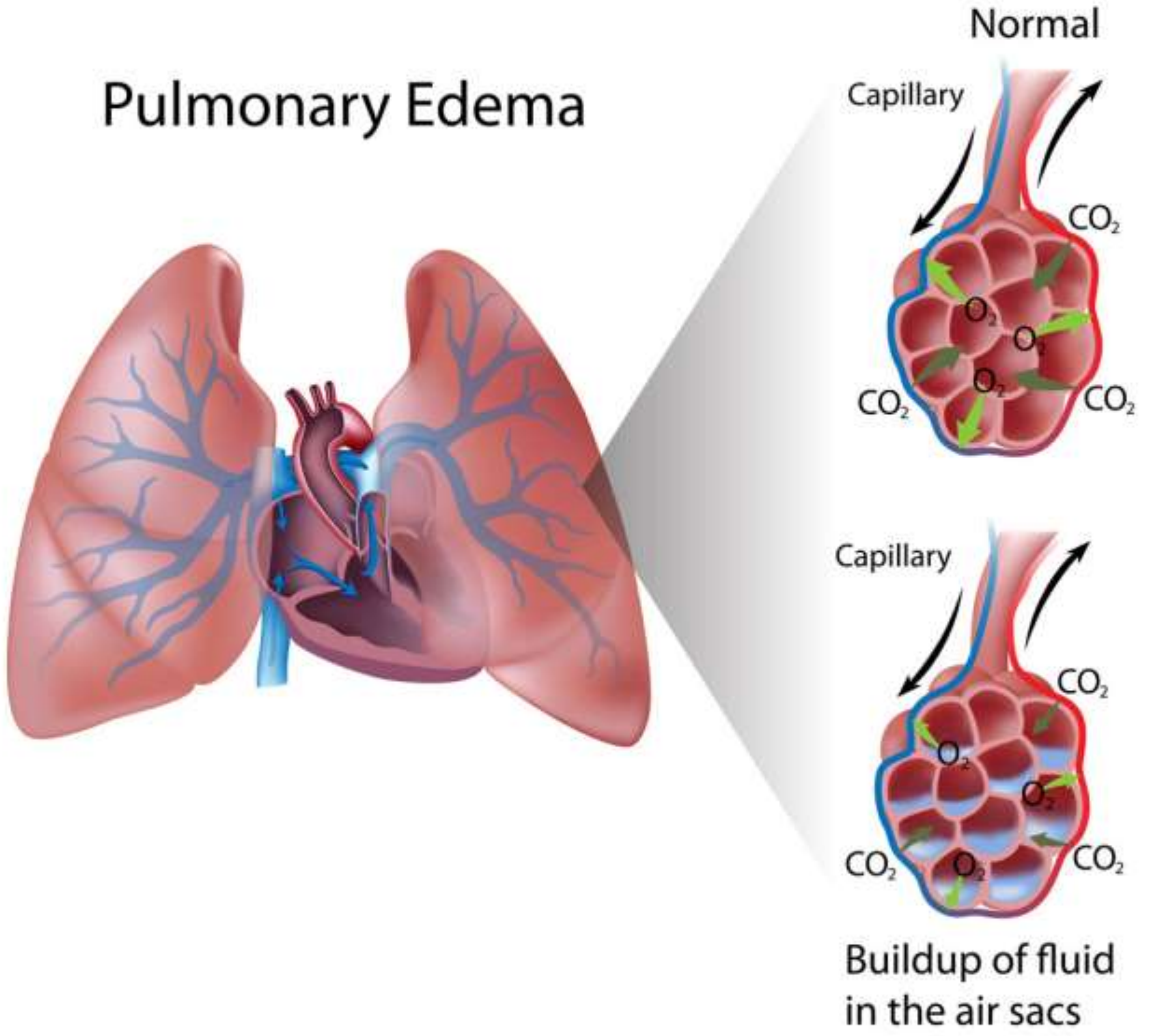
ii. Pulmonary edema

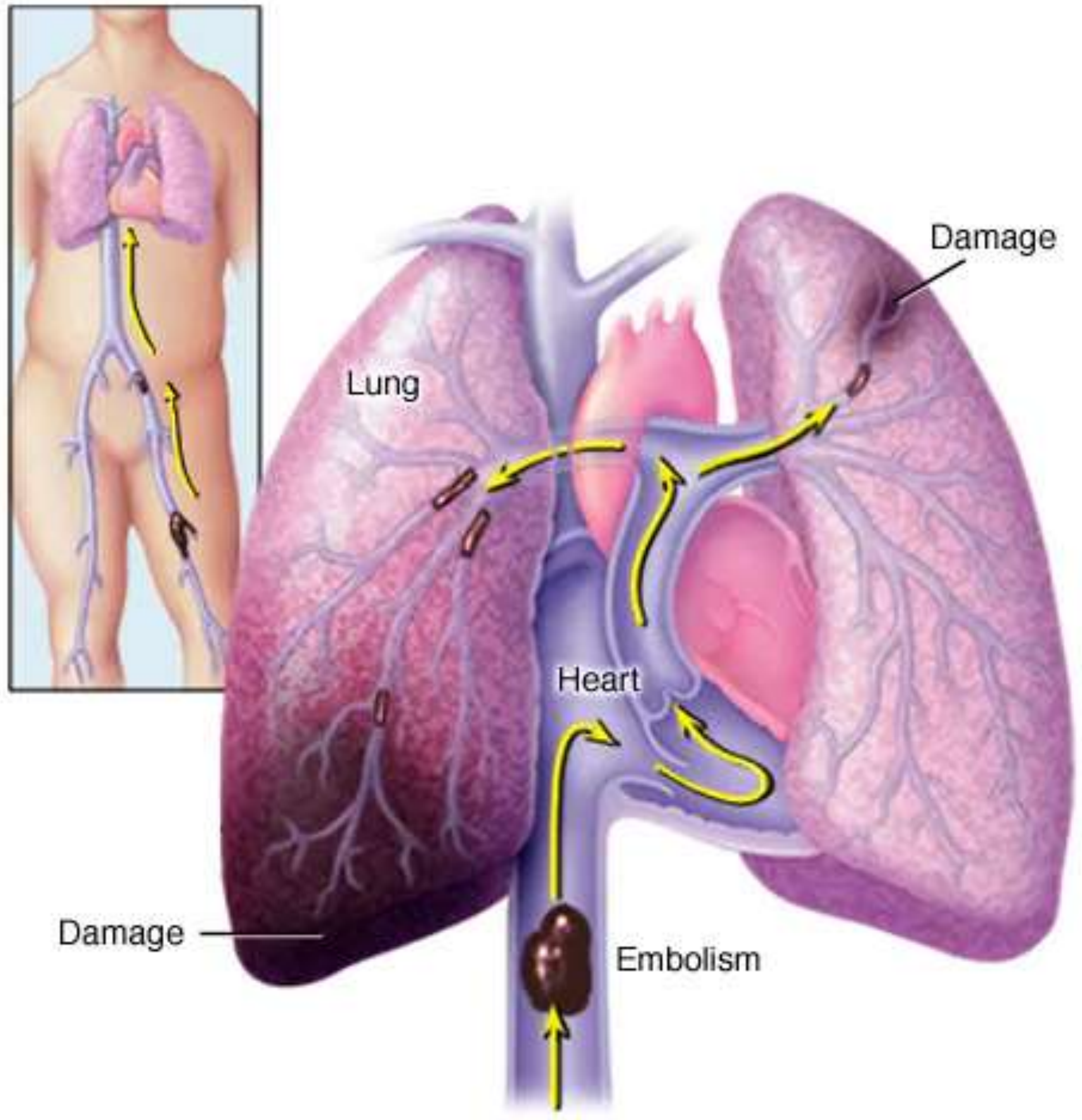
iii. Pneumonia

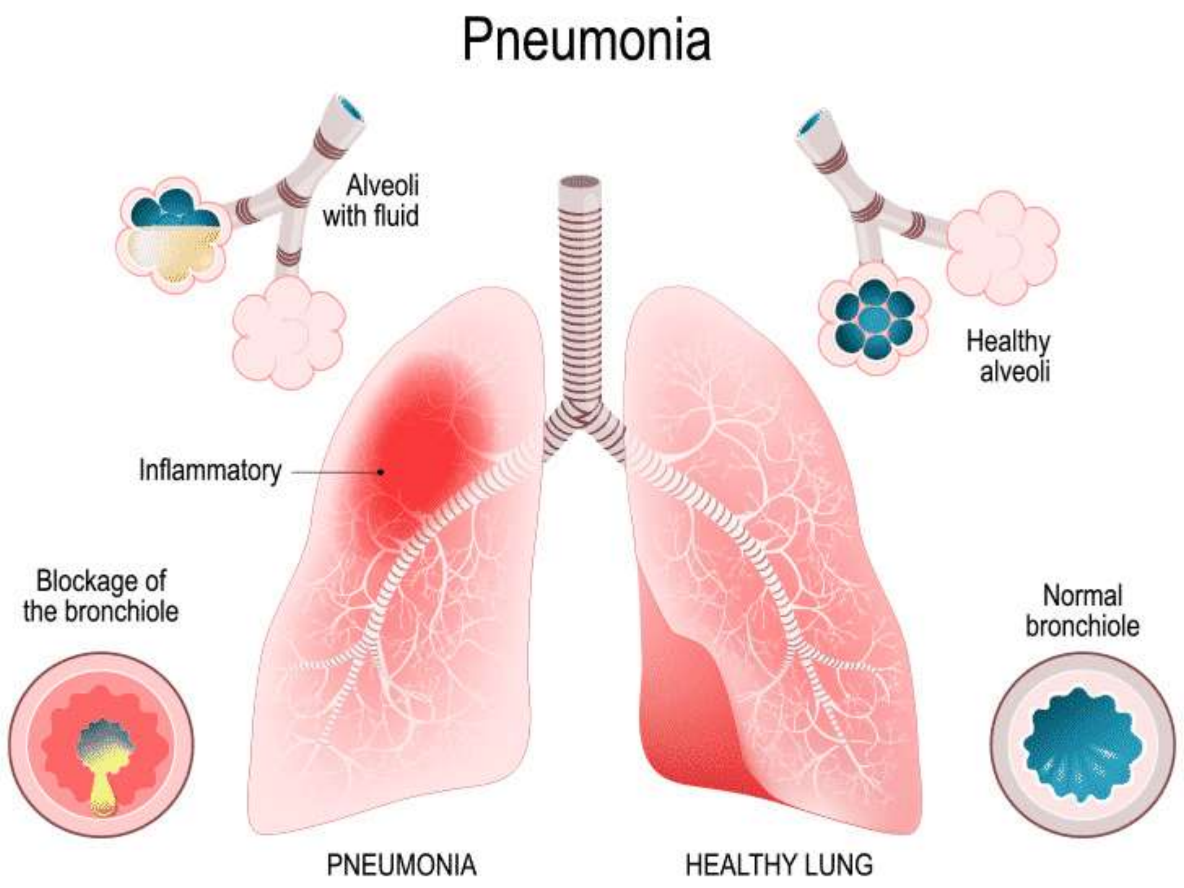
iv. Over inflation of lungs

v. Microembolism in pulmonary capillaries

vi. Stimulation by exogenous and endogenous chemical substances such as histamine, halo thane, bradykinin, serotonin and phenyldiguanide.


Pulmonary Edema
Normal
Capillary
CO_2
O_2
Capillary
Buildup of fluid
in the air sacs


Lung
Damage
Heart
Damage
Embolism


Pneumonia
Alveoli
with fluid
Healthy
alveoli
Inflammatory
Blockage of
the bronchiole
Normal
bronchiole
PNEUMONIA
HEALTHY LUNG

EFFECT OF STIMULATION OF ‘J’ RECEPTORS

Stimulation of the ‘J’ receptors produces a reflex response, which is characterized by apnea.

Apnea is followed by **hyperventilation, bradycardia, hypotension and weakness of skeletal muscles**.

Role of ‘J’ receptors in physiological conditions is not clear.

However, these receptors are responsible for **hyperventilation in patients affected by pulmonary congestion and left heart failure**.

4. IMPULSES FROM IRRITANT RECEPTORS OF LUNGS

Besides stretch receptors, there is another type of receptors in the bronchi and bronchioles of lungs, called irritant receptors.

Irritant receptors are stimulated by irritant chemical agents such as **ammonia and sulfur dioxide.**

These receptors send afferent impulses to respiratory centers via **vagal nerve fibers**.

Stimulation of irritant receptors produces reflex hyperventilation along with bronchospasm.

Hyperventilation along with bronchospasm prevents further entry of harmful agents into the alveoli.

5. IMPULSES FROM BARORECEPTORS

Baroreceptors or pressoreceptors are the receptors which give response to change in blood pressure.

FUNCTION

Baroreceptors in carotid sinus and arch of aorta give response to increase in blood pressure.

Whenever arterial blood pressure increases, baroreceptors are activated and send inhibitory impulses to vasomotor center in medulla oblongata.

This causes decrease in blood pressure and inhibition of respiration.

However, in physiological conditions, **the role of baroreceptors in regulation of respiration** is insignificant.

6. IMPULSES FROM CHEMORECEPTORS

Chemoreceptors play an important role in the chemical regulation of respiration.

7. IMPULSES FROM PROPRIOCEPTORS

Proprioceptors are the receptors which give response to change in the position of body.

These receptors are situated in joints, tendons and muscles.

Proprioceptors are stimulated during the muscular exercise and send impulses to brain, particularly cerebral cortex, through somatic afferent nerves.

Cerebral cortex in turn causes hyperventilation by sending impulses to medullary respiratory centers.

8. IMPULSES FROM THERMORECEPTORS

Thermoreceptors are cutaneous receptors, which give response to change in the environmental temperature.

Thermoreceptors are of two types, namely receptors for cold and receptors for warmth.

When body is exposed to cold or when cold water is applied over the body, cold receptors are stimulated and send impulses to cerebral cortex via somatic afferent nerves.

Cerebral cortex in turn, stimulates the **respiratory centers and causes hyperventilation**

9. IMPULSES FROM PAIN RECEPTORS

Pain receptors are those which give response to **pain stimulus**.

Whenever pain receptors are stimulated, the impulses are sent to cerebral cortex via somatic afferent nerves.

Cerebral cortex in turn, stimulates the respiratory centers and causes hyperventilation.

CHEMICAL MECHANISM

Chemical mechanism of regulation of respiration is operated through the chemoreceptors.

Chemoreceptors are the sensory nerve endings, which give response to changes in chemical constituents of **blood.**

Changes in Chemical Constituents of Blood which Stimulate Chemoreceptors

1. Hypoxia (decreased pO2)

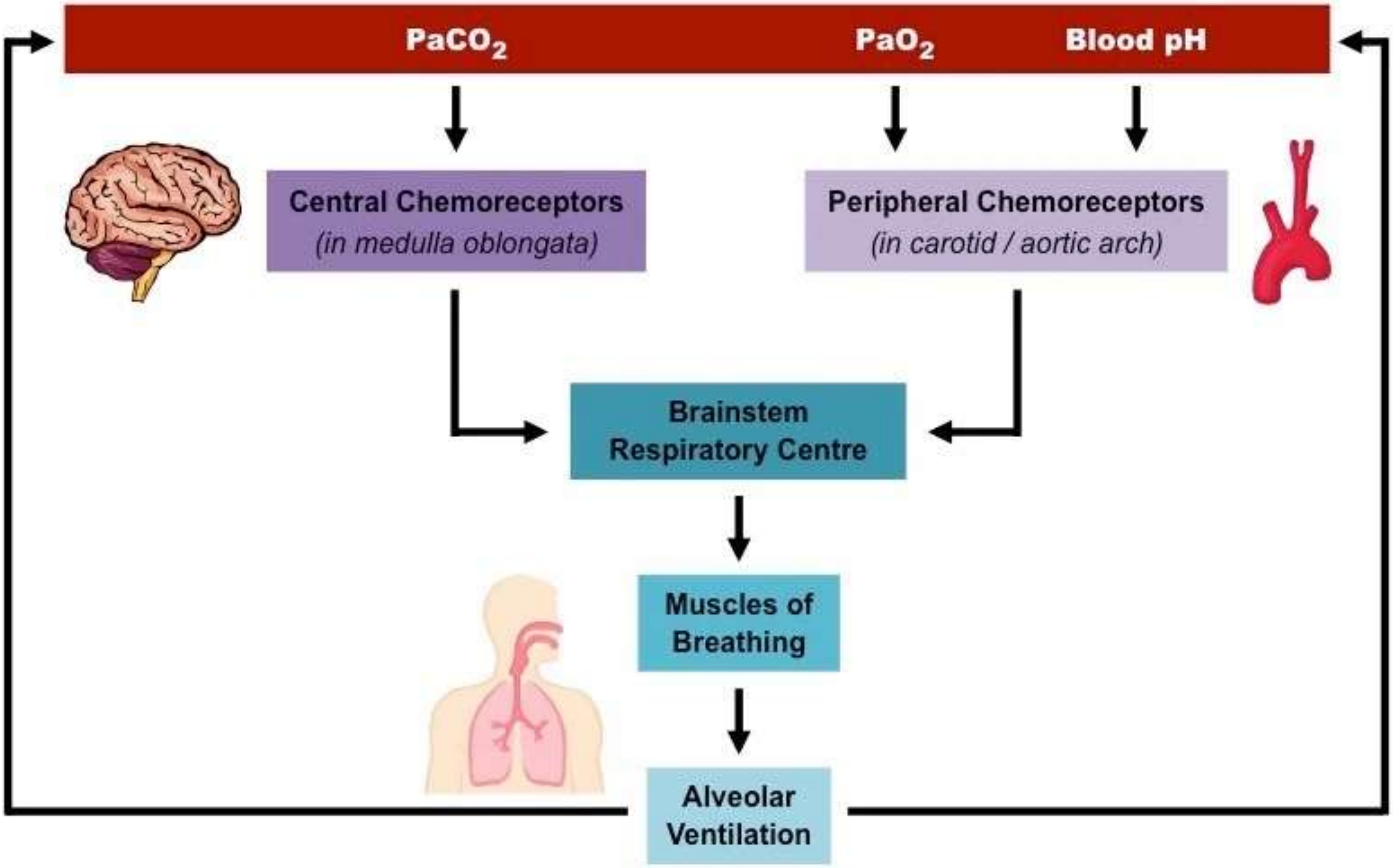
2. Hypercapnea (increased pCO2)

3. Increased hydrogen ion concentration.

Types of Chemoreceptors Chemoreceptors are classified into two groups:

1. Central chemoreceptors

2. Peripheral chemoreceptors.


PaCO2
PaO2
Blood pH
Central Chemoreceptors
(in medulla oblongata)
Peripheral Chemoreceptors
(in carotid / aortic arch)
Brainstem
Respiratory Centre
Muscles of
Breathing
Alveolar
Ventilation

CENTRAL CHEMORECEPTORS

Central chemoreceptors are the chemoreceptors present in the brain.

SITUATION

Central chemoreceptors are situated in deeper part of medulla oblongata, close to the dorsal respiratory group of neurons.

This area is known as chemosensitive area and the neurons are called chemoreceptors.

Chemo receptors are in close contact with blood and cerebrospinal fluid

Mechanism of Action

Central chemoreceptors are connected with respiratory centers, particularly the dorsal respiratory group of neurons through synapses.

These chemoreceptors act slowly but effectively. Central chemoreceptors are responsible for 70% to 80% of increased ventilation through chemical regulatory mechanism.

Main stimulant for central chemoreceptors is the **increased hydrogen ion concentration.**

However, if hydrogen ion concentration **increases in the blood**, it cannot stimulate the central chemoreceptors because, the **hydrogen ions from blood cannot cross the bloodbrain barrier and blood-cerebrospinal fluid barrier**

On the other hand, if carbon dioxide increases in the blood, it can easily cross the blood-brain barrier and bloodcerebrospinal fluid barrier and enter the interstitial fluid of brain or the cerebrospinal fluid.

There, the carbon dioxide combines with water to form carbonic acid.

Since carbonic acid is unstable, it immediately dissociates into hydrogen ion and bicarbonate ion.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Hydrogen ions stimulate the **central chemoreceptors.**

From chemoreceptors, the excitatory impulses are sent to dorsal respiratory group of neurons, resulting in increased ventilation (increased rate and force of breathing).

Because of this, excess carbon dioxide is washed out and respiration is brought back to normal.

Lack of oxygen does not have significant effect on the central chemoreceptors, except that it generally depresses the overall function of brain

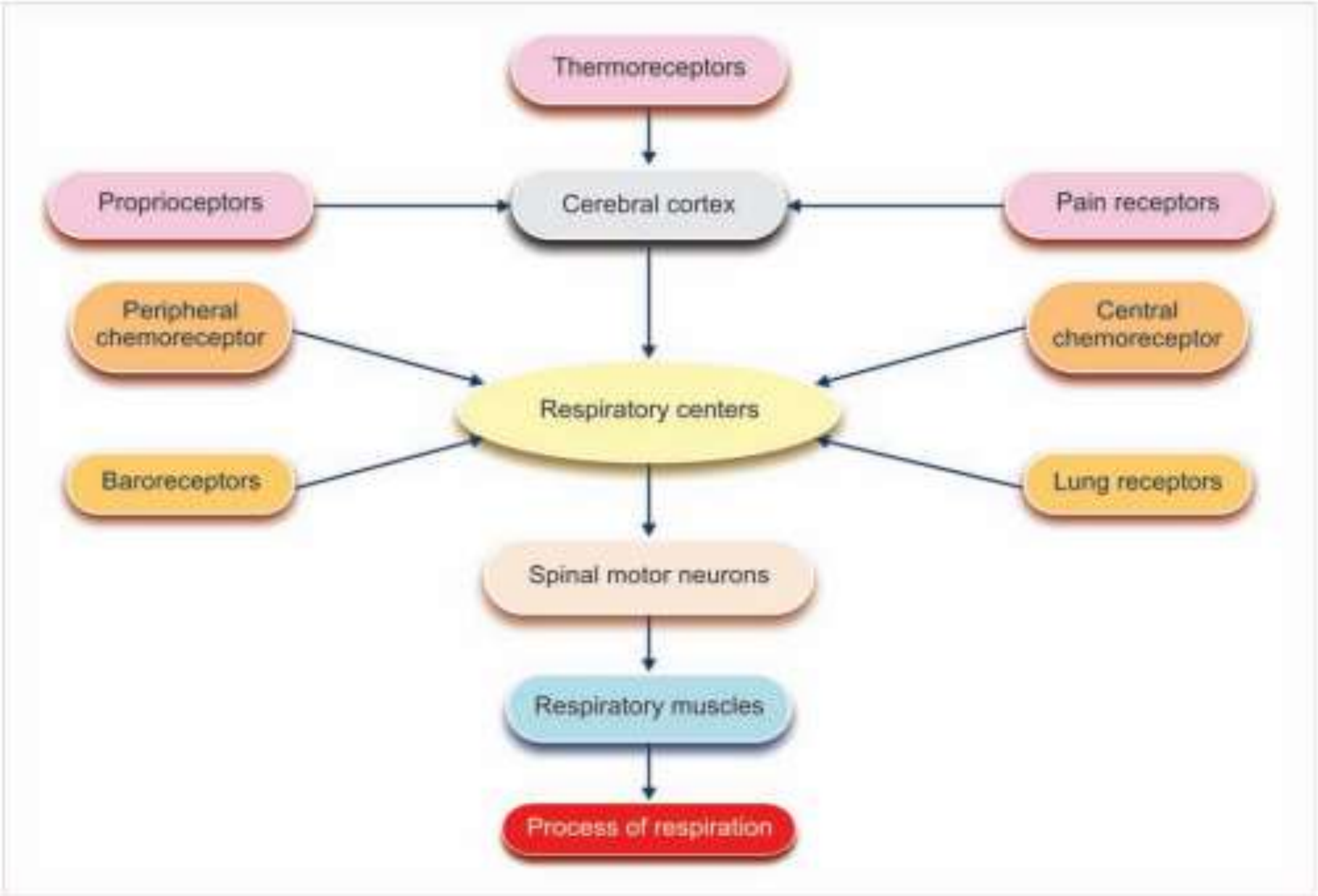


FIGURE 126.3: Factors affecting respiratory centers

PERIPHERAL CHEMORECEPTORS

Peripheral chemoreceptors are the chemoreceptors present in carotid and aortic region.

MECHANISM OF ACTION

Hypoxia is the most potent stimulant for peripheral chemoreceptors.
It is because of the presence of oxygen sensitive potassium channels in the glomus cells of peripheral chemoreceptors.

Hypoxia causes closure of oxygen sensitive potassium channels and prevents potassium efflux.

This leads to **depolarization of glomus cells (receptor potential) and generation of action potentials in nerve ending**.

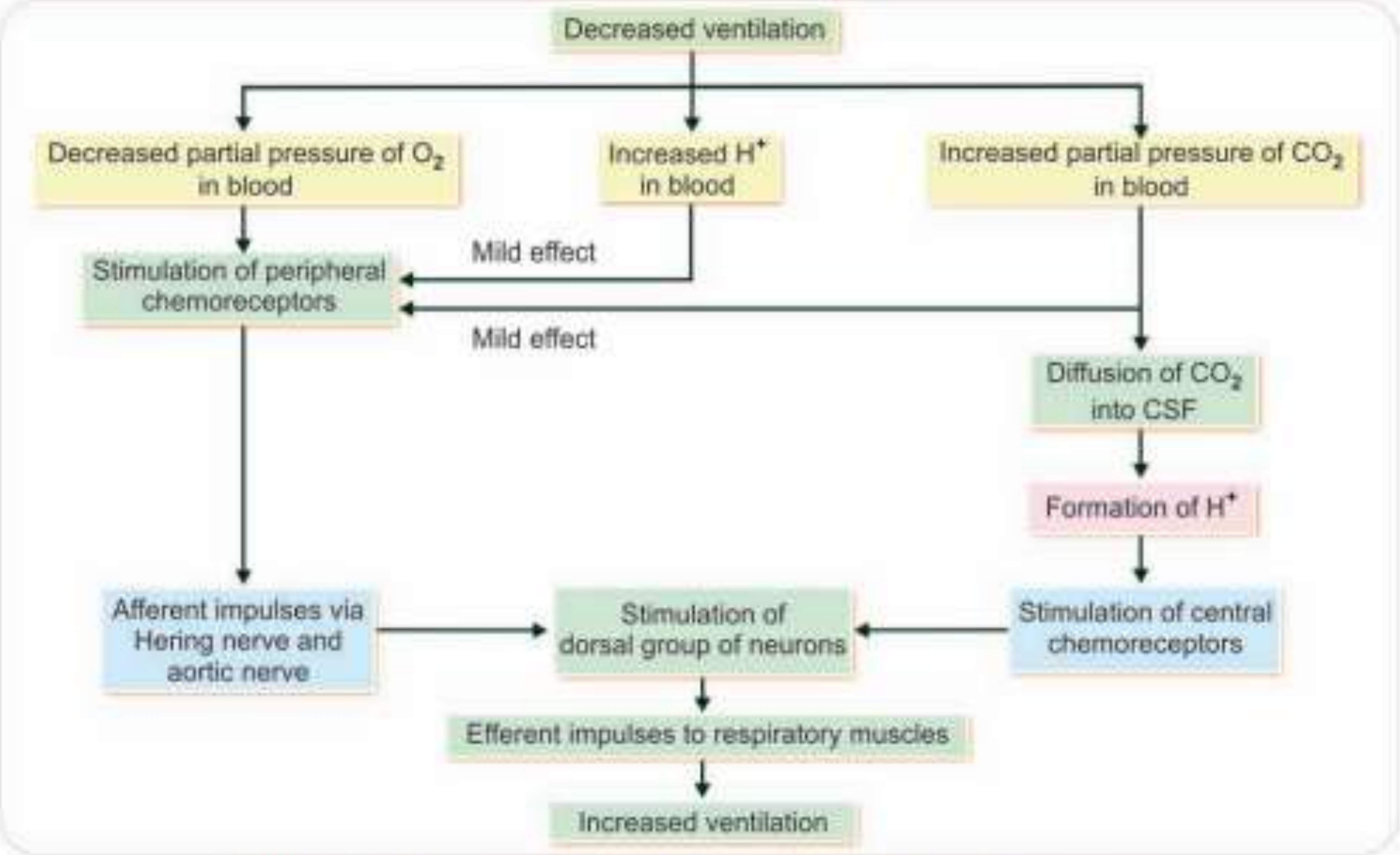


FIGURE 126.4: Chemical regulation of respiration. CSF = Cerebrospinal fluid.

These impulses pass through aortic and Hering nerves and excite the dorsal group of neurons.

Dorsal group of neurons in turn, send excitatory impulses to respiratory muscles, resulting in increased ventilation.

This provides enough oxygen and rectifies the lack of oxygen.

In addition to hypoxia, peripheral chemoreceptors are also stimulated by hypercapnea and increased hydrogen ion concentration.

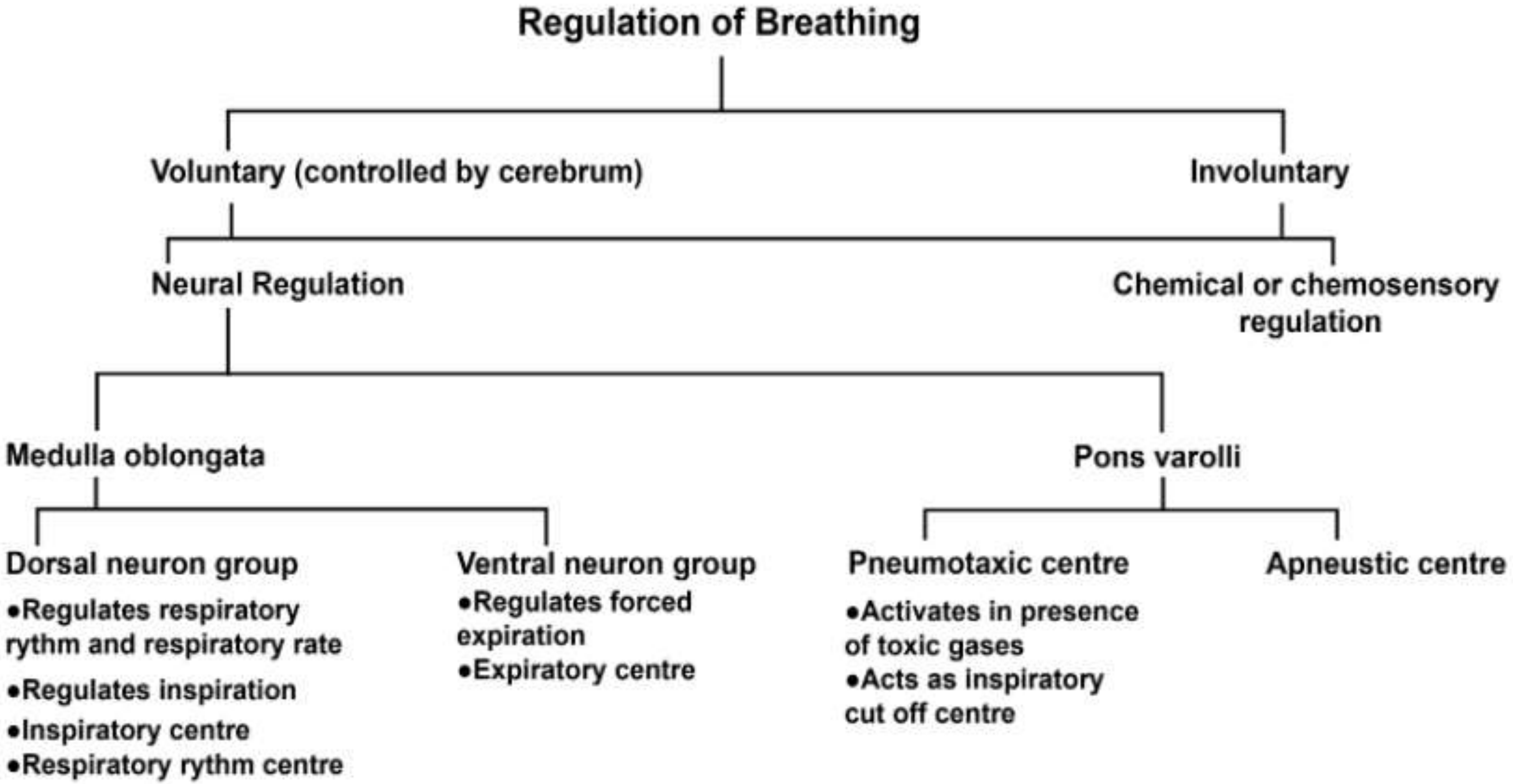
However, the sensitivity of peripheral chemoreceptors to **hypercapnea and increased hydrogen ion concentration is mild.**

Regulation of Respiration

Objective:

To maintain normal levels of PO_2 & PCO_2 in arterial blood.

Respiratory control system: Three basic elements:-


Regulation of Breathing
Voluntary (controlled by cerebrum)
Involuntary
Neural Regulation
Chemical or chemosensory regulation
Medulla oblongata
Pons varolli
Dorsal neuron group
•Regulates respiratory rythm and respiratory rate
•Regulates inspiration
•Inspiratory centre
•Respiratory rythm centre
Ventral neuron group
•Regulates forced expiration
•Expiratory centre
Pneumotaxic centre
•Activates in presence of toxic gases
•Acts as inspiratory cut off centre
Apneustic centre