B.Sc. (H) Biochemistry
IVth Sem (2019-20)
Human Physiology
Regulation of respiration
Lecture 7 & 8

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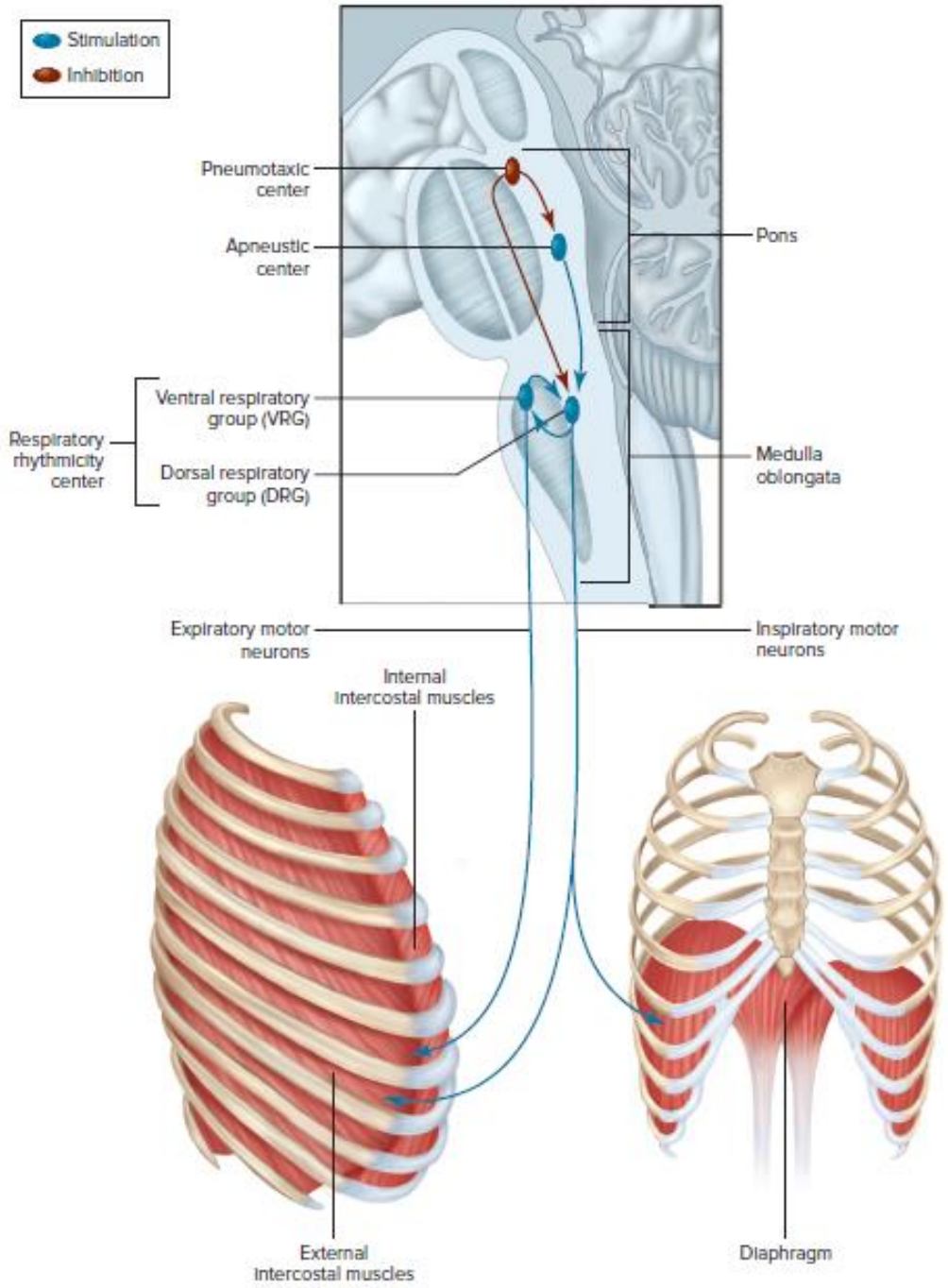
Control of Respiration:
Neural Generation of rhythmic breathing

- Breathing depends entirely upon cyclical respiratory muscle excitation of the diaphragm and the intercostal muscles by their motor neurons.
- Inspiration is initiated by a burst of action potentials in the spinal motor neurons to inspiratory muscles like the diaphragm. Then the action potentials cease, the inspiratory muscles relax, and expiration occurs as the elastic lungs recoil.
- In situations such as exercise when the contraction of expiratory muscles facilitates expiration, the neurons to these muscles, which were not active during inspiration, begin firing during expiration.

Dorsal respiratory group (DRG)

- Control of this neural activity resides primarily in neurons in the medulla oblongata, There are two main anatomical components of the **medullary respiratory center**.
- The neurons of the **dorsal respiratory group** (**DRG**) primarily fire during inspiration and have input to the spinal motor neurons that activate respiratory muscles involved in inspiration—the diaphragm and inspiratory intercostal muscles. The primary inspiratory muscle at rest is the diaphragm, which is innervated by the phrenic nerves.

Brainstem centers which control the respiratory rate and depth



- Inspiratory motor neurons are driven primarily by the DRG while expiratory motor neurons (active mostly during forced expiration and strenuous exercise) are driven primarily by the VRG.
- DRG and VRG innervate each other allowing phasic inspiration and expiration.
- The centers in the upper pons are primarily responsible for fine-tuning respiratory control.

Ventral respiratory group (VRG)

- The **ventral respiratory group** (**VRG**) is the other main complex of neurons in the medullary respiratory center. The **respiratory rhythm generator** is located in the **pre-Bötzinger complex** of neurons in the upper part of the VRG. This rhythm generator appears to be composed of pacemaker cells and a complex neural network that, acting together, set the basal respiratory rate.

Ventral respiratory group (VRG)..

- The VRG contains expiratory neurons that appear to be most important when large increases in ventilation are required (for example, during strenuous physical activity). During active expiration, motor neurons activated by the expiratory output from the VRG cause the expiratory muscles to contract.
- This helps to rapidly move air out of the lungs rather than depending only on the passive expiration that occurs during quiet breathing.

- During quiet breathing, the respiratory rhythm generator activates inspiratory neurons in the DRG that depolarize the inspiratory spinal motor neurons, causing the inspiratory muscles to contract.
- When the inspiratory motor neurons stop firing, the inspiratory muscles relax, allowing passive expiration.
- During increases in breathing, the inspiratory and expiratory motor neurons and muscles are not activated at the same time but, rather, alternate in function.

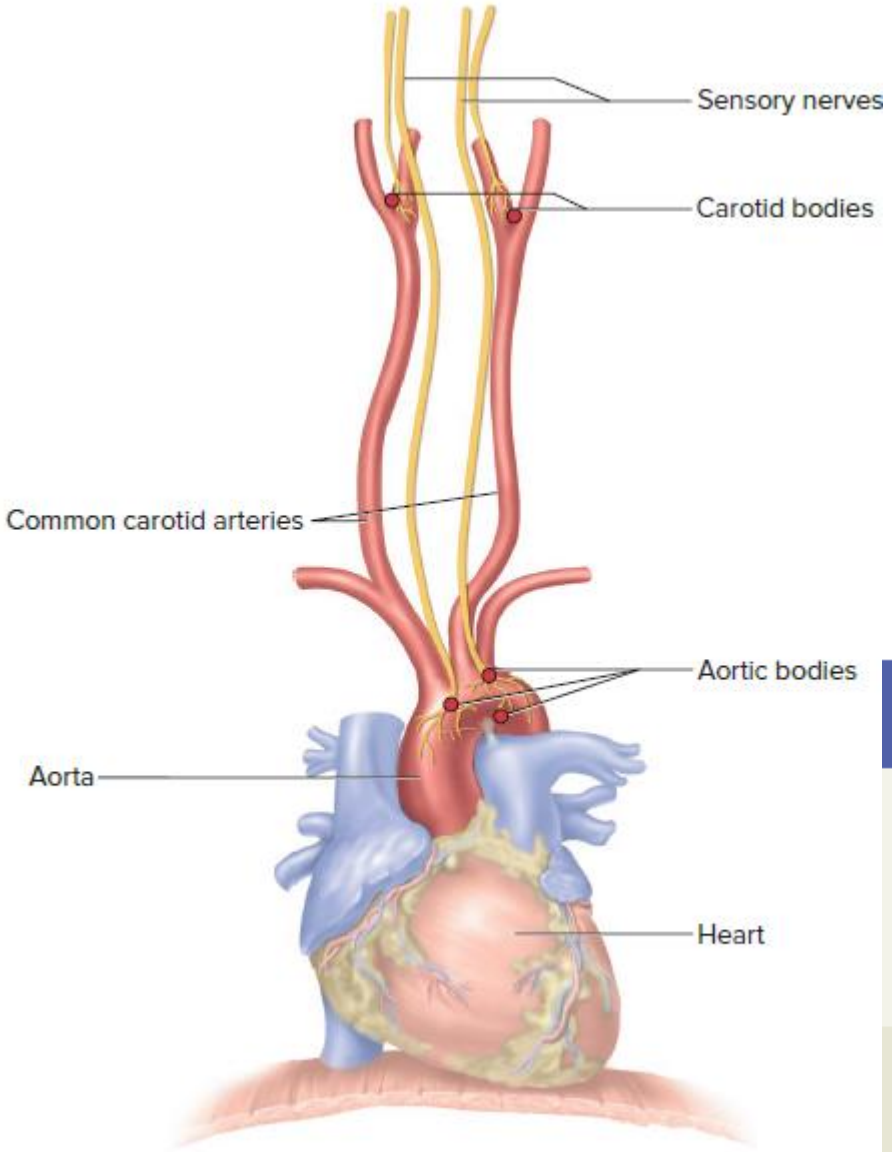
- The medullary inspiratory neurons receive a rich synaptic input from neurons in various areas of the pons, the part of the brainstem just above the medulla.
- This input fine-tunes the output of the medullary inspiratory neurons and may help terminate inspiration by inhibiting them. It is likely that an area of the lower pons called the **apneustic center** is the major source of this output, whereas an area of the upper pons called the **pneumotaxic center** modulates the activity of the apneustic center. The pneumotaxic center, also known as the **pontine respiratory group,** helps to smooth the transition between inspiration and expiration.
- The respiratory nerves in the medulla and pons also receive synaptic input from higher centers of the brain such that the pattern of respiration is controlled voluntarily during speaking, diving, and even with emotions and pain.

Hering–Breuer reflex.

- Another cutoff signal for inspiration comes from **pulmonary stretch receptors,** which lie in the airway smooth muscle layer and are activated by a large lung inflation.
- Action potentials in the afferent nerve fibers from the stretch receptors travel to the brain and inhibit the activity of the medullary inspiratory neurons. This is called the **Hering–Breuer reflex.** This allows feedback from the lungs to terminate inspiration by inhibiting inspiratory nerves in the DRG. However, this reflex is important in setting respiratory rhythm only under conditions of very large tidal volumes, as in strenuous exercise.
- The arterial chemoreceptors (next slide) also have important input to the respiratory control centers such that the rate and depth of respiration can be increased when the levels of arterial oxygen decrease, or when arterial carbon dioxide or H^+ concentration increases.
- A final point about the medullary inspiratory neurons is that they are quite sensitive to inhibition by sedatives-hypnotics (such as barbiturates) and opiates (such as morphine, heroin, and fentanyl). Death from an overdose of these drugs is often due directly to a cessation of breathing.

Control of Ventilation by P_{O2}, P_{CO2}, and H^+ Concentration: Chemoreceptors

- Respiratory rate and tidal volume are not fixed but can be increased or decreased over a wide range.
- There are many inputs to the medullary inspiratory neurons, but the most important for the automatic control of ventilation at rest come from peripheral (arterial) chemoreceptors and central chemoreceptors.
- The **peripheral chemoreceptors,** located high in the neck at the bifurcation of the common carotid arteries and in the thorax on the arch of the aorta) are called the **carotid bodies** and **aortic bodies,** respectively. In both locations, they are quite close to, but distinct from, the arterial baroreceptors and are in intimate contact with the arterial blood.



Location of the carotid and aortic bodies. Each carotid body is quite close to a carotid sinus, the major arterial baroreceptor. Both right and left common carotid bifurcations contain a carotid sinus and a carotid body.

TABLE **Major Stimuli for the Central and Peripheral Chemoreceptors**

Peripheral chemoreceptors—carotid bodies and aortic bodies—respond to changes in the arterial blood. They are stimulated by

- Significantly decreased P_{O_2} (hypoxia)
- Increased H^+ concentration (metabolic acidosis)
- Increased P_{CO_2} (respiratory acidosis)

Central chemoreceptors—located in the medulla oblongata—respond to changes in the *brain extracellular fluid*. They are stimulated by increased P_{CO_2} via associated changes in H^+ concentration (see equation 13–11).

- The carotid bodies, in particular, are strategically located to monitor oxygen supply to the brain.
- The peripheral chemoreceptors are composed of specialized receptor cells stimulated mainly by a decrease in the arterial P_{O2} and an increase in the arterial H^+ concentration
- These cells communicate synaptically with neuron terminals from which afferent nerve fibers pass to the brainstem. There they provide excitatory synaptic input to the medullary inspiratory neurons.
- The carotid body input is the predominant peripheral chemoreceptor involved in the control of respiration.

- The **central chemoreceptors** are located in the medulla and, like the peripheral chemoreceptors, provide excitatory synaptic input to the medullary inspiratory neurons. They are stimulated by an increase in the H+ concentration of the brain's extracellular fluid. Such changes result mainly from changes in blood $\boldsymbol{P_{CO2}}$.

Control by P_{O2}

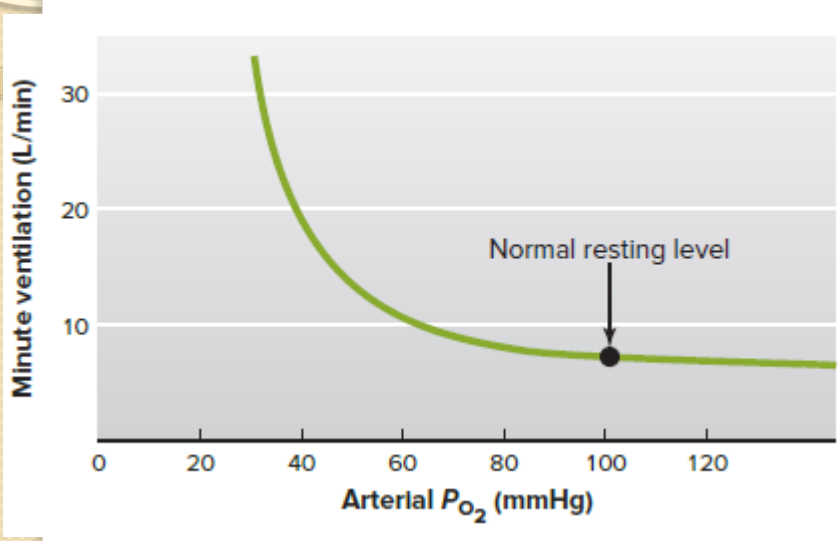
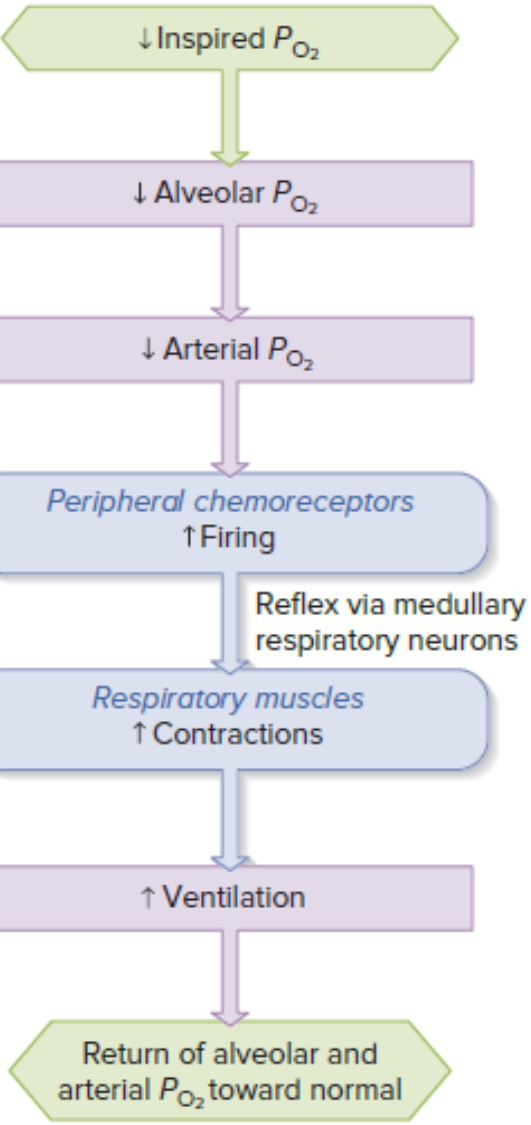


Fig: It illustrates an experiment in which healthy subjects breathe low-P_{O_2} gas mixtures for several minutes. The experiment is performed in a way that keeps arterialP_{CO_2} constant so that the pure effects of changing only P_{O_2} can be studied.

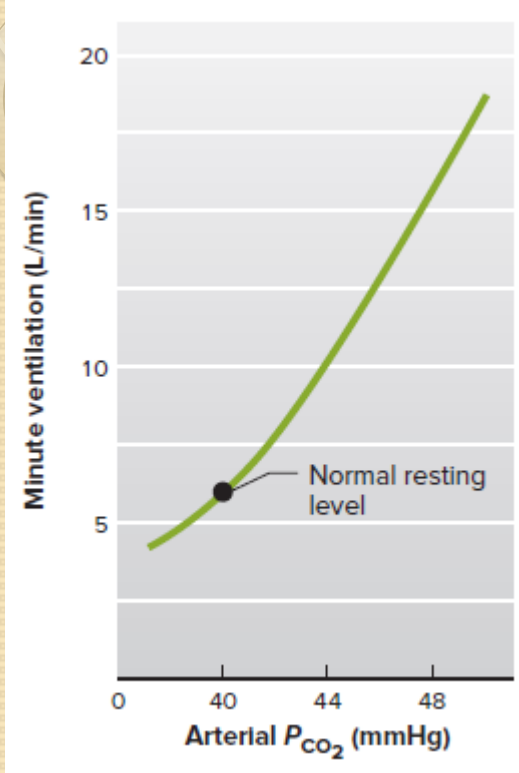
- Little increase in ventilation is observed until the oxygen concentration of the inspired air is reduced enough to lower arterial P_{O_2} to 60 mmHg. Beyond this point, any further decrease in arterial P_{O_2} causes a marked reflex increase in ventilation.



- This reflex is mediated by the peripheral chemoreceptors. The low arterial P_{O_2} increases the rate at which the receptors discharge, resulting in an increased number of action potentials traveling up the afferent nerve fibers and stimulating the medullary inspiratory neurons.
- The resulting increase in ventilation provides more oxygen to the alveoli and minimizes the decrease in alveolar and arterial P_{O_2} produced by the low- P_{O_2} gas mixture.

- Total oxygen transport by the blood is not really decreased very much until the arterial P_{O_2} decreases below about 60 mmHg. Therefore, increased ventilation would not result in much more oxygen being added to the blood until that point is reached.
- To reiterate, the peripheral chemoreceptors respond to decreases in arterial P_{O_2}, as occurs in lung disease or exposure to high altitude. However, the peripheral chemoreceptors are *not* stimulated in situations in which modest reductions take place in the oxygen *content* of the blood but no change occurs in arterial P_{O_2}.
- Anemia is a decrease in the amount of hemoglobin present in the blood without a decrease in arterial P_{O_2}, because the concentration of dissolved oxygen in the arterial blood is normal

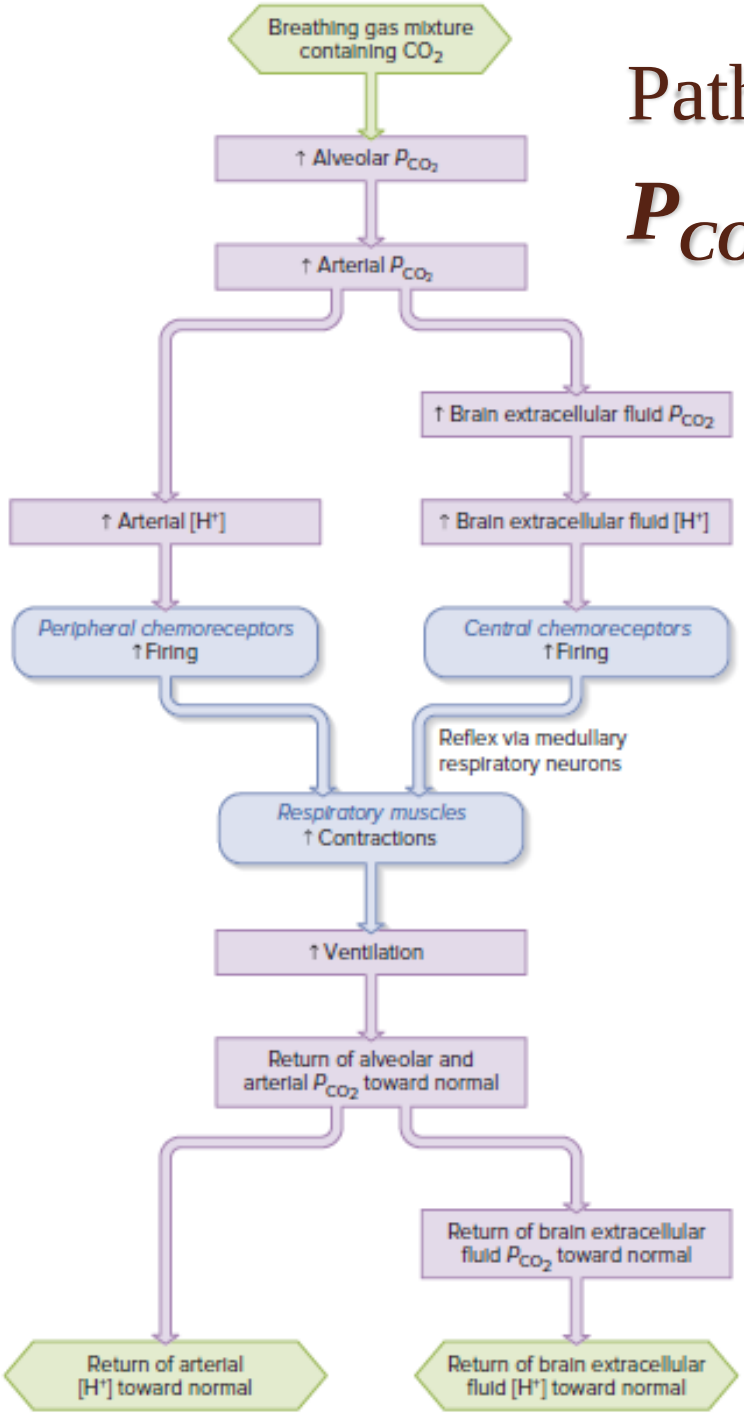
Control by P_{CO_2}



Fir: This illustrates an experiment in which subjects breathe air with variable quantities of carbon dioxide added. The presence of carbon dioxide in the inspired air causes an increase in alveolarP_{CO_2}, and therefore the diffusion gradient for CO_2 is reversed from the normal situation. This results in a net uptake of CO_2 from the alveolar air and, therefore, an increase in arterial PP_{CO_2}, .

Note that even a very small increase in arterial PCO_2 causes a marked reflex increase in ventilation. Experiments like this have documented that the reflex mechanisms controlling ventilation prevent small increases in arterial PCO_2 to a much greater degree than they prevent equivalent decreases in arterial PO_2.

- Some pulmonary diseases, such as emphysema, can cause the body to retain carbon dioxide, resulting in an increase in arterial P_{CO_2} that stimulates ventilation. This promotes the elimination of the carbon dioxide. Conversely, if arterial P_{CO_2} decreases below normal levels for whatever reason, this removes some of the stimulus for ventilation. This decreases ventilation and allows metabolically produced carbon dioxide to accumulate, thereby returning the P_{CO_2} to normal. In this manner, the arterial P_{CO_2} is stabilized near the normal value of 40 mmHg.



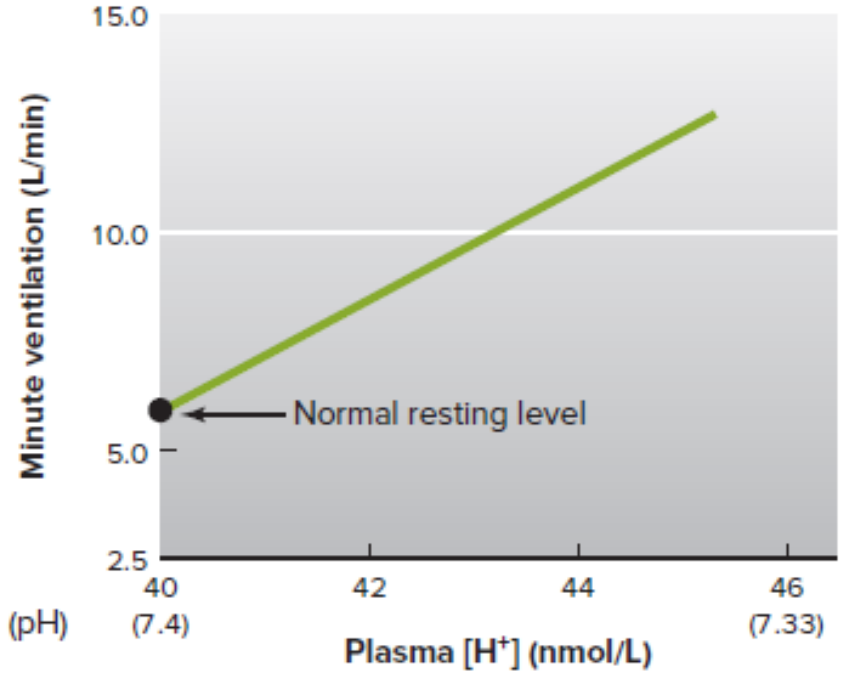
Pathways by which increased arterial P_{CO2} stimulates ventilation.

- The ability of changes in arterial P_{CO_2}, to reflexively control ventilation is largely due to associated changes in H+ concentration
- Both the peripheral and central chemoreceptors initiate the pathways that mediate these reflexes.
- The peripheral chemoreceptors are stimulated by the increased arterial H+ concentration resulting from the increased P_{CO_2}, . At the same time, because carbon dioxide diffuses rapidly across the membranes separating capillary blood and brain interstitial fluid, the increase in arterial P_{CO_2}, causes a rapid increase in brain extracellular fluid P_{CO_2}, . This increased P_{CO_2}, increases brain extracellular fluid H+ concentration, which stimulates the central chemoreceptors.

- Inputs from both the peripheral and central chemoreceptors stimulate the medullary inspiratory neurons to increase ventilation. The end result is a return of arterial and brain extracellular fluid P_{CO_2}, and H+ concentration toward normal.
- Of the two sets of receptors involved in this reflex response to increases in P_{CO_2}, , the central chemoreceptors are the more important, accounting for about 70% of the increased ventilation.
- The effects of increased P_{CO_2}, an decreased P_{O_2}, not only exist as independent inputs to the medulla but potentiate each other's effects. The acute ventilatory response to combined low P_{O_2}, and high P_{CO_2}, is considerably greater than the sum of the individual responses.
- Very high levels of carbon dioxide actually *inhibit* ventilation and may be lethal. This is because such concentrations of carbon dioxide act directly on the medulla to inhibit the respiratory neurons by an anesthesia-like effect. Other symptoms caused by very high blood P_{CO_2}, include severe headaches, restlessness, and dulling or loss of consciousness.

Control by Changes in Arterial H^+ Concentration That Are Not Due to Changes in Carbon Dioxide

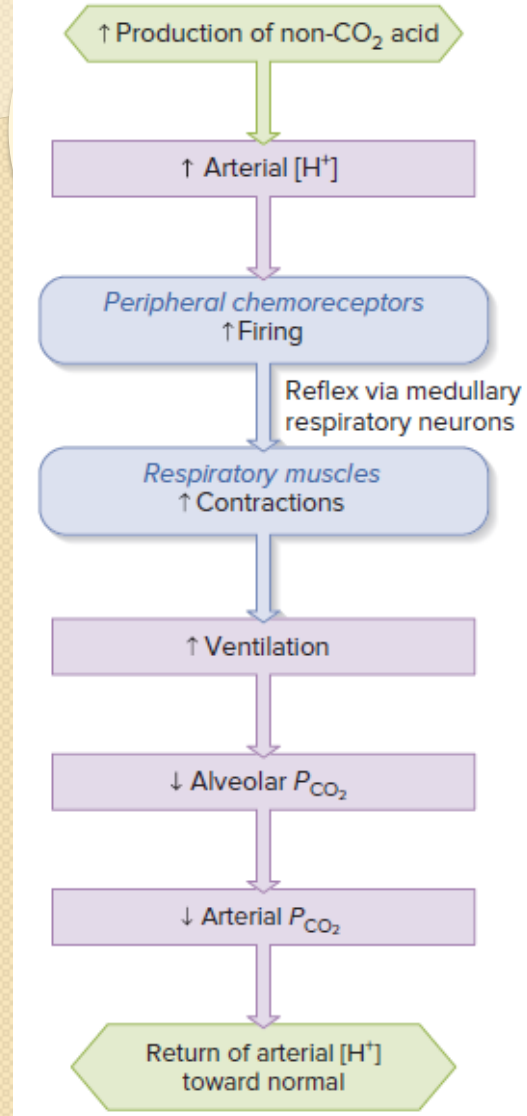
- It is established that Retention or excessive elimination of carbon dioxide causes respiratory acidosis and respiratory alkalosis, respectively. There are, however, many normal and pathological situations in which a change in arterial H^+ concentration is due to some cause other than a primary change in P_{CO_2}, . This is termed ***metabolic acidosis*** when H+ concentration is increased and ***metabolic alkalosis*** when it is decreased.



- Changes in ventilation in response to an increase in plasma H^+ concentration produced by the administration of lactic acid.

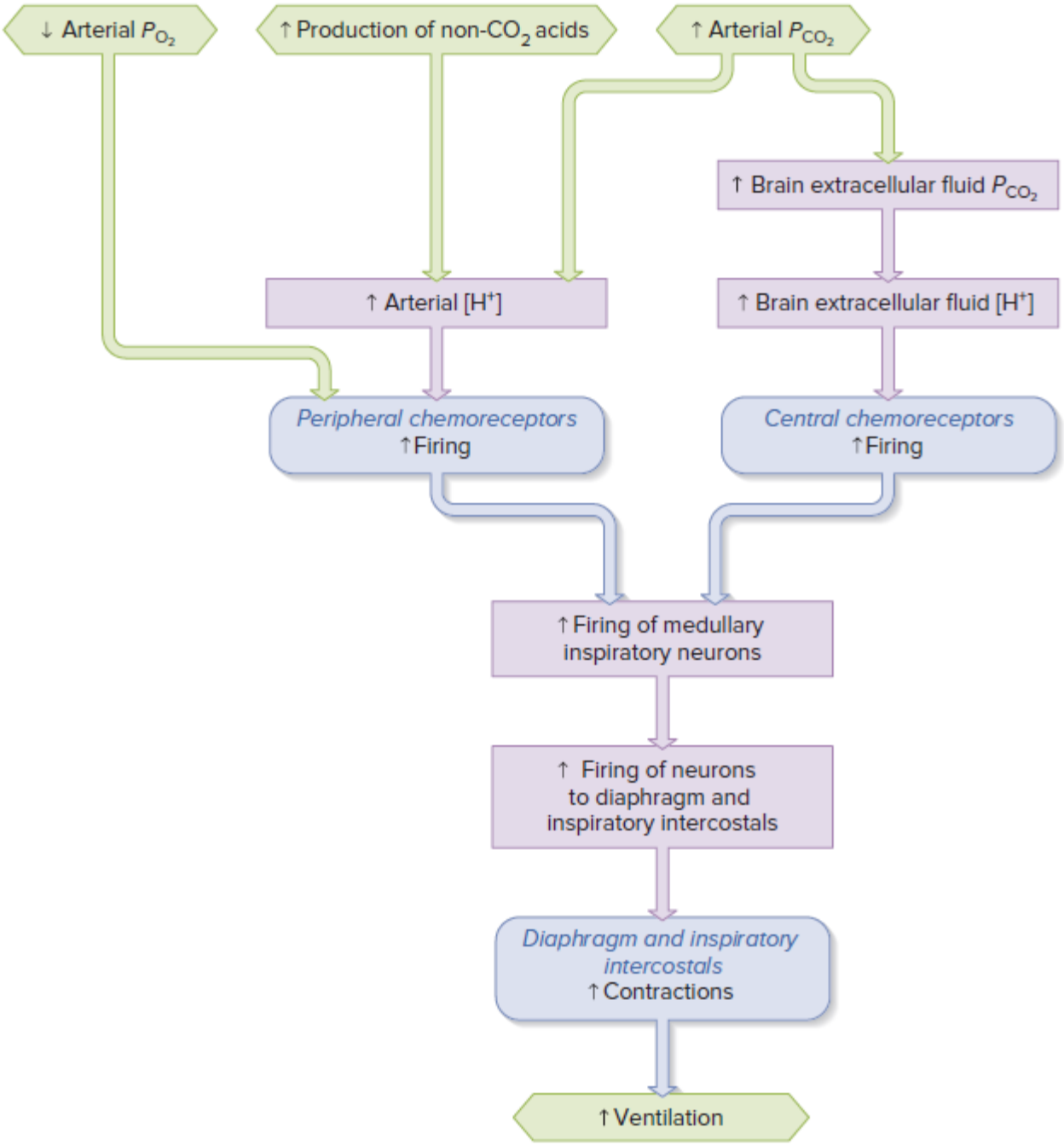
- In such cases, the peripheral chemoreceptors provide the major afferent inputs to the brain in altering ventilation. For example, the addition of lactic acid to the blood, as in strenuous exercise, causes hyperventilation almost entirely by stimulation of the peripheral chemoreceptors.
- The central chemoreceptors are only minimally stimulated in this case because brain H^+ concentration is increased to only a small extent, at least early on, by the H^+ generated from the lactic acid.
- This is because H^+ penetrates the blood–brain barrier very slowly. In contrast, as described earlier, carbon dioxide penetrates the blood– brain barrier easily and changes brain H^+ concentration.

Effect of H^+ ions on respiration



Reflexively induced hyperventilation minimizes the change in arterial H^+ concentration when acids are produced in excess in the body. Note that under such conditions, arterial $\boldsymbol{P_{CO2}}$ is reflexively reduced below its normal value.

- The converse of the previous situation is also true: When arterial H+ concentration is decreased by any means other than by a reduction in P_{CO_2}, (for example, by the loss of H^+ from the stomach when vomiting), ventilation is reflexively depressed because of decreased peripheral chemoreceptor output. The increased ventilation induced by a metabolic acidosis reduces arterial P_{CO_2}, , which decreases arterial H^+ concentration back toward normal. Similarly, hypoventilation induced by a metabolic alkalosis results in an increase in arterial P_{CO_2}, and consequently a restoration of H^+ concentration toward normal.
- When a change in arterial H^+ concentration due to some acid unrelated to carbon dioxide influences ventilation via the peripheral chemoreceptors, P_{CO_2}, is displaced from normal.
- This is a reflex that regulates arterial H^+ concentration at the expense of changes in arterial P_{CO_2}, . Maintenance of normal arterial H^+ is necessary because nearly all enzymes of the body function best at physiological pH.



Summary of the major chemical inputs that stimulate ventilation. When arterial P_{O_2}, increases or when P_{CO_2}, or H^+ concentration decreases, ventilation is reflexively decreased.

CONTROL OF VENTILATION DURING EXCERSISE

- During exercise, the alveolar ventilation may increase as much as 20-fold.
- On the basis of our three variables—P_{O_2}, , P_{CO_2}, , and H^+ concentration—it may seem easy to explain the mechanism that induces this increased ventilation.
- This is not the case, however, and the major stimuli to ventilation during exercise, at least moderate exercise, remain unclear.

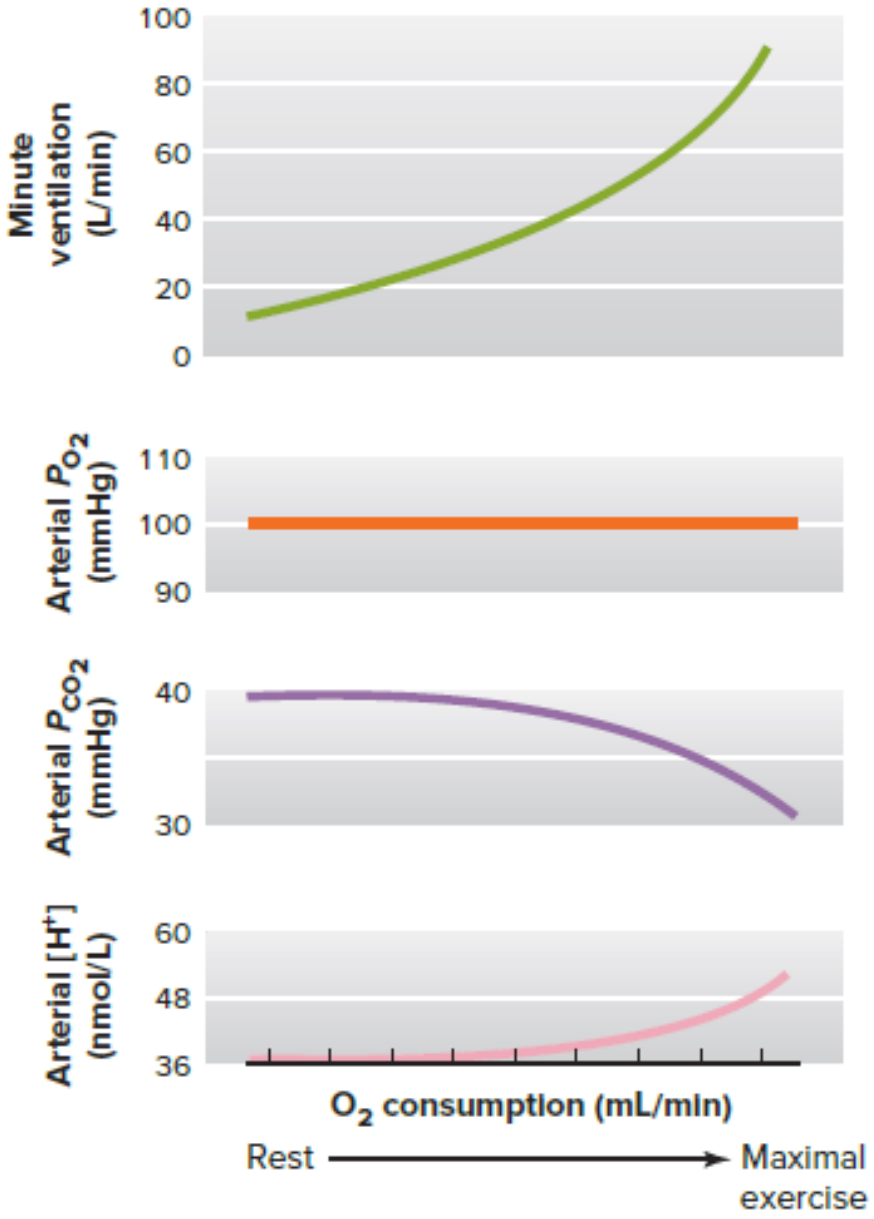
Increased P_{CO_2} as the Stimulus?

- It would seem logical that, as the exercising muscles produce more carbon dioxide, blood P_{CO_2} would increase. This is true, however, only for systemic *venous* blood but not for systemic *arterial* blood.
- Why is it that arterialP_{CO_2} does not increase during exercise? There are two factors from the section on alveolar gas pressures:

(1) Arterial P_{CO_2} is determined by alveolar P_{CO_2}, and

(2) Alveolar P_{CO_2} is determined by the ratio of carbon dioxide production to alveolar ventilation.

- During moderate exercise, the alveolar ventilation increases in exact proportion to the increased carbon dioxide production, so alveolar and therefore arterial P_{CO_2} do not change. In fact, in very strenuous exercise, the alveolar ventilation increases relatively more than carbon dioxide production.
- In other words, during strenuous exercise, a person may hyperventilate; thus, alveolar and systemic arterial P_{CO_2} may actually decrease alveolar and therefore arterial P_{CO_2} do no change.

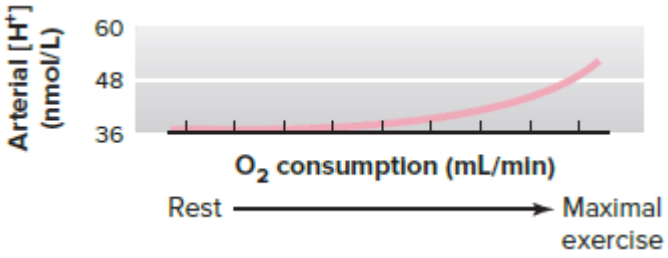


The effect of exercise on ventilation, arterial gas pressures, and H^+ concentration. All these variables remain constant during moderate exercise; any change occurs only during strenuous exercise, when the person is actually hyperventilating (decrease in P_{CO_2}).

Decreased P_{O_2} as the Stimulus?

- The story is similar for oxygen. Although systemic *venous* P_{O_2} decreases during exercise due to an increase in oxygen consumption in the tissues, alveolar P_{O_2} and, therefore, systemic *arterial* P_{O_2} usually remain unchanged
- This is because cellular oxygen consumption and alveolar ventilation increase in exact proportion to each other, at least during moderate exercise.
- In healthy individuals, ventilation is not the limiting factor in strenuous exercise—cardiac output is. Ventilation can increase enough to maintain arterial P_{O_2}.

Increased H^+ Concentration as the Stimulus?



- Because the arterial P_{O_2} does not change during moderate exercise and decreases during strenuous exercise, there is no accumulation of excess H^+ resulting from carbon dioxide accumulation.
- However, during strenuous exercise, there *is* an increase in arterial H^+ concentration due to the generation and release of lactic acid into the blood. This change in H^+ concentration is responsible, in part, for stimulating the hyperventilation accompanying strenuous exercise.

Other Factors

- A variety of other factors are involved in stimulating ventilation during exercise. These include

(1) Reflex input from mechanoreceptors in joints and muscles,

(2) An increase in body temperature,

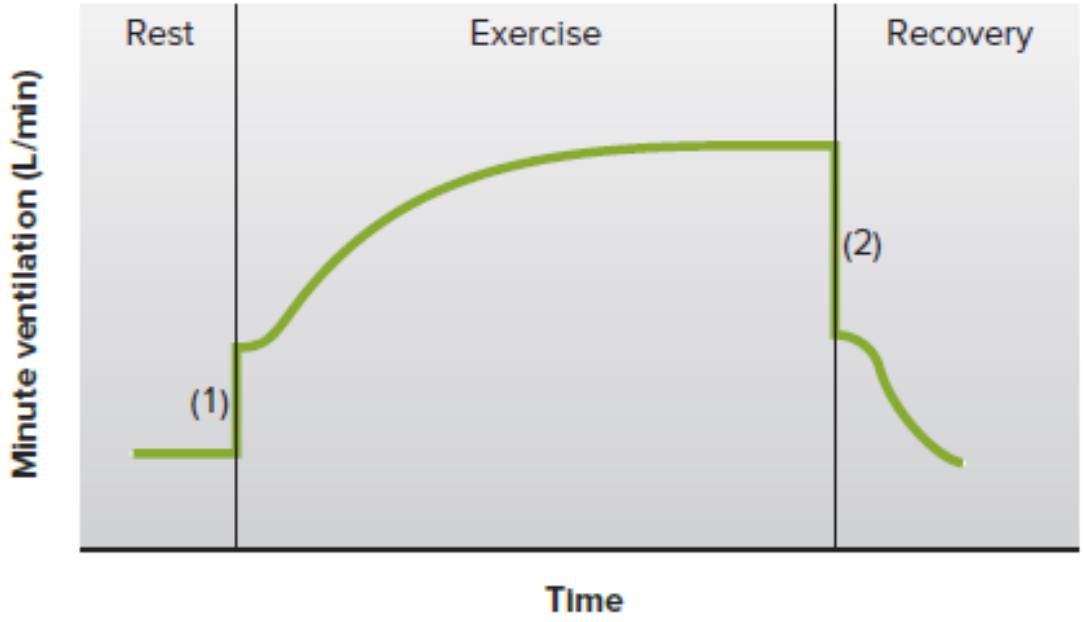
(3) Inputs to the respiratory neurons via branches from axons descending from the brain to motor neurons supplying the exercising muscles (central command),

(4) An increase in the plasma epinephrine concentration,

(5) An increase in the plasma K^+ concentration due to movement of K^+ out of the exercising muscles, and

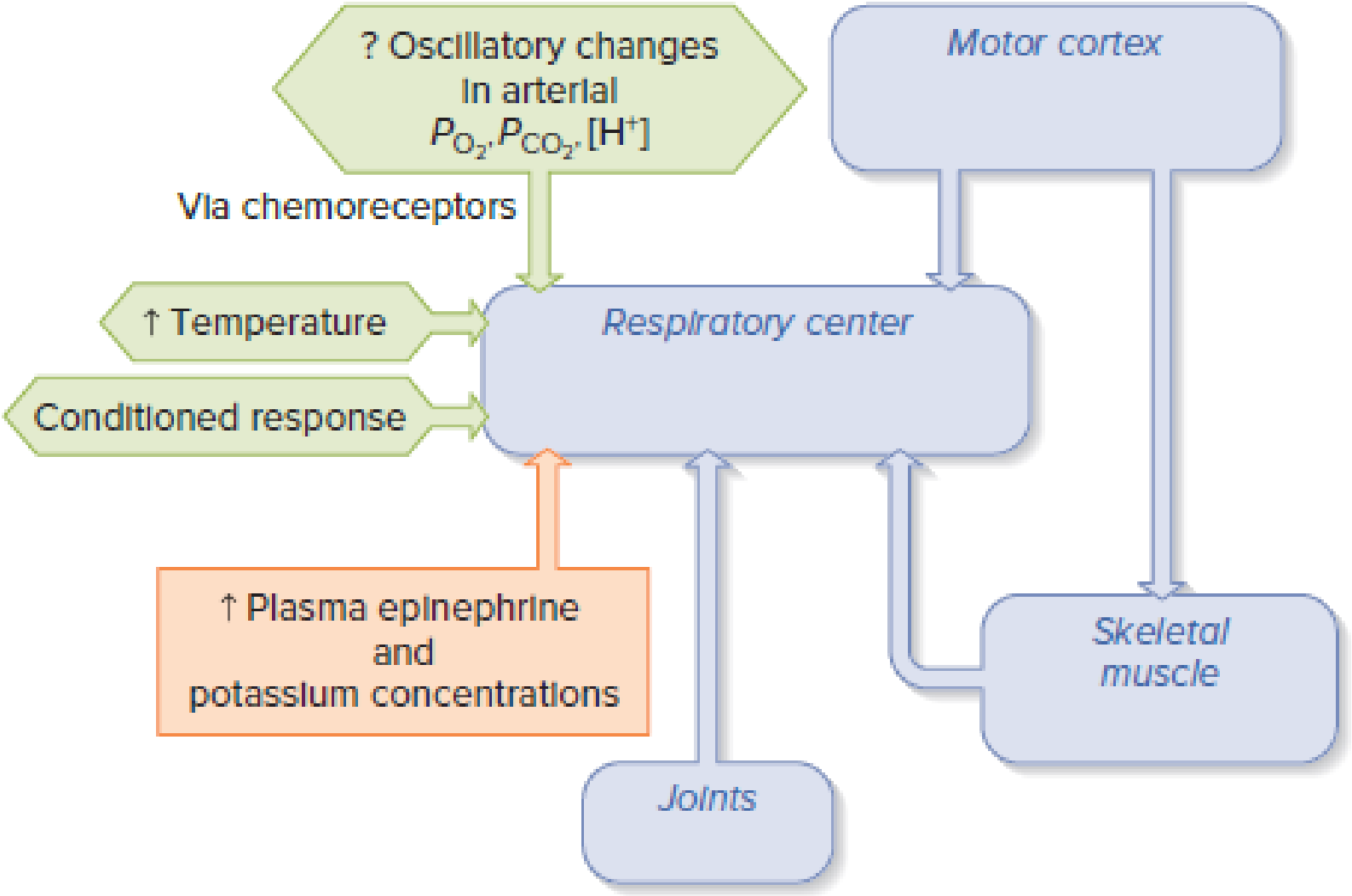
(6) A conditioned (learned) response mediated by neural input to the respiratory centers.

Ventilation changes during exercise.



Factors (1) and (3) (from prvious slide) are most likely to be significant. There is an abrupt increase—within seconds—in ventilation at the onset of exercise and an equally abrupt decrease at the end; these changes occur too rapidly to be explained by alteration of chemical constituents of the blood or by altered body temperature.

Summary of factors that stimulate ventilation during exercise.



Voluntary Control of Breathing

- It is accomplished by descending pathways from the cerebral cortex to the motor neurons of the respiratory muscles.
- This voluntary control of respiration cannot be maintained when the involuntary stimuli, such as an increased P_{CO_2} or H^+ concentration, become intense. An example is the inability to hold breath for very long.
- The opposite of breath holding—deliberate hyperventilation—lowers alveolar and arterial P_{CO_2} and increases P_{O_2}. Swimmers sometimes voluntarily hyperventilate immediately before underwater swimming to be able to hold their breath longer. But sometimes low P_{CO_2} may still permit breath holding at a time when the exertion is decreasing the arterial P_{O_2} to levels that can cause unconsciousness and lead to drowning.
- Besides the obvious forms of voluntary control, respiration must also be controlled during such complex actions as speaking, singing, and swallowing.

Reflexes from J Receptors

- In the lungs, either in the capillary walls or the interstitium, are a group of sensory receptors called **J receptors.** They are normally dormant but are stimulated by an increase in lung interstitial pressure caused by the collection of fluid in the interstitium.
- Such an increase occurs during the vascular congestion caused by either occlusion of a pulmonary vessel (called a ***pulmonary embolism***) or left ventricular heart failure, as well as by strenuous exercise in healthy people.
- The main reflex effects are rapid breathing (tachypnea) and a dry cough. In addition, neural input from J receptors gives rise to sensations of pressure in the chest and ***dyspnea***—the feeling that breathing is labored or difficult.

References

Vander's human physiology (2019) 15th ed., Widmaier, E.P., Raff, H. And strang, K.T., Mcgraw hill international publications (new york), ISBN: 978-1-259-90388-5