CONTROL OF BREATHING

The motor neurons that stimulate the respiratory muscles are controlled by two major descending pathways: one that controls voluntary breathing and another that controls involuntary breathing. The unconscious rhythmic control of breathing is influenced by sensory feedback from receptors sensitive to the P CO2, pH, and P O2 of cerebrospinal fluid and arterial blood, and also pressure in the bronchial tree (the mass of bronchioles and the bronchi) that is connected to the brain by the vagus nerve.

Inspiration and expiration are produced by the contraction and relaxation of skeletal muscles in response to activity in somatic motor neurons from the spinal cord. The activity of these motor neurons is controlled, in turn, by descending tracts from neurons in the respiratory control centres in the medulla oblongata and from neurons in the cerebral cortex.

<u>Anatomy of the system.</u>

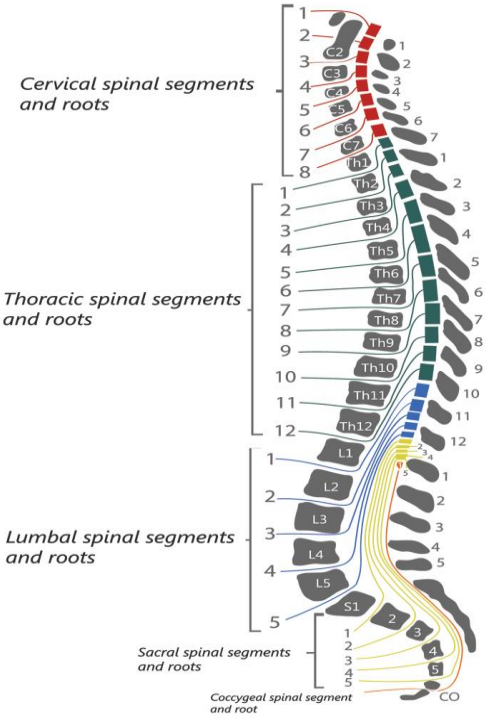
A. Spinal motoneurones.

The somatic (sensory) motor neurons that stimulate the respiratory muscles including the thoracic nerves and phrenic nerves have their cell bodies in the grey matter of the spinal cord. The motoneurones of the phrenic nerve (bundle of axons of the phrenic neurones), stimulating the diaphragm, have cell bodies in the cervical level of the spinal cord while the thoracic nerves that innervate the respiratory muscles of the rib cage and abdomen have cell bodies in the thoracolumbar region of the cord. These spinal motoneurons are regulated, either directly or via spinal interneurons, by descending axons from the brain.

The thoracic nerves. There are 12 pairs of thoracic nerves, which arise from the thoracolumbar region of the spinal cord which comprises of the thoracic (T1 – T12) and lumbar (L1 – L5) spinal segments. The thoracic nerves are divided into two groups:

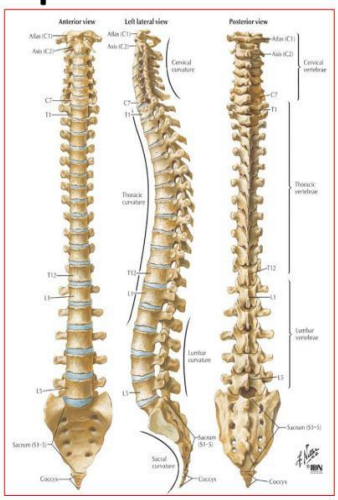
1. Intercostal nerves (T1 – T11). These run between ribs and supply muscles and skin of the chest and abdominal walls.
2. Subcostal nerves (T12, 12^{th} thoracic nerve pair). These nerves run below the 12^{th} rib and supply the muscles and skin of the abdominal wall.

Phrenic nerves. Phrenic nerves are only a pair of nerves arising from the cervical spine (C3 – C5) and descending through the neck and thorax to innervate the diaphragm, the primary muscle responsible for breathing. They stimulate the diaphragm to contract, allowing inhalation, and also transmit sensory information from the diaphragm and pleura (lung lining) to the brain. There are two phrenic nerves, one on each side of the body, which innervate the corresponding half of the diaphragm. Any damage to the phrenic nerve can lead to diaphragmatic paralysis, making breathing difficult or impossible.



Thoracolumbar Spine

- The anatomy of the thoracolumbar spine is a combination of vertebrae, intervertebral joints, ligaments/tendons, muscles, nerves and vascular supply.
- The thoracic region consists of **12** vertebrae. Due to its articulations with rib cage, the thoracic spine is more rigid than the cervical and lumbar regions.
- The lumbar spine is made up of **5** vertebrae. It is designed to be strong, protecting the spinal cord and spinal nerve roots. At the same time, it is highly flexible, providing mobility in many different planes including flexion, extension, lateral flexion, and rotation.



Note the curvatures in thoracic (primary, concave anteriorly) and lumbar (secondary, convex anteriorly) spine

Dr. Zeenat & Dr. Vohra

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B. Brain Stem Respiratory Centres

Medulla Oblongata and Pons

The control of breathing is managed by a group of neurons collectively known as the respiratory centre, located bilaterally in the medulla oblongata and pons of the brainstem. This respiratory centre is divided into three functional areas: the medullary rhythmicity area, and the pneumotaxic area and the apneustic area in the pons region. These areas work together to regulate the rhythm and depth of breathing.

Medullary Rhythmicity Area

The medullary rhythmicity area, located in ventrolateral region of the medulla oblongata, is responsible for controlling the basic automatic rhythm of respiration. It contains both inspiratory and expiratory neurons (I and E neurones each comprising of two types of neurones) in the inspiratory and expiratory areas respectively.

Roles of the respiratory centres

A large collection of inspiratory neurons (I) only forms the dorsal respiratory group and the pre-BotZinger Complex (preBotC) of the medulla. These send axons that directly stimulate the spinal motoneurons of respiration, causing inspiration. There is also a ventral respiratory group of neurons in the medulla that contains both I and E neurons. The inspiratory neurons (I) located here indirectly stimulate the spinal motoneurones of respiration via spinal interneurons. There

is also a region of densely packed expiratory neurons in the ventral respiratory group. These E neurons inhibit the motoneurons of the phrenic nerve during expiration. The activity of the I and E neurons varies in a reciprocal way to produce a rhythmic pattern of breathing.

The inspiratory area of the medulla has an intrinsic self-paced rhythm of firing impulses. This means that even in absence of external inputs or sensory feedback, the preBotC can still generate a rhythmic pattern of activity. This intrinsic rhythm is thought to be rise from a complex interplay of cellular and network properties, including pacemaker cells, synaptic interactions, and ion channel dynamics, which altogether generate a self-sustaining oscillatory activity that drives breathing.

Note: The key difference between the dorsal ventral group and the PreBotC is that while PreBotC acts as the primary pacemaker, intrinsically generating the rhythmic drive for inspiration and setting the basic respiratory rhythm, DRG modulates this rhythm established by the preBotC by integrating sensory feedback from the body, adjusting the depth and rate of breathing in response to changes in blood gas levels and mechanical lung feedback, making the DRG most important when it comes to adapting to physiological changes.

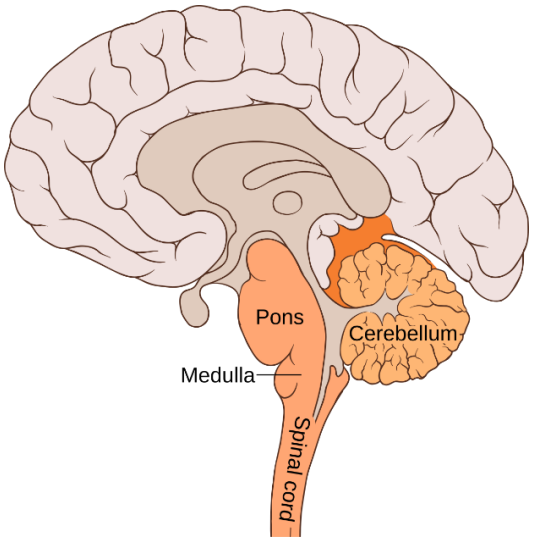
Therefore, in studying the control of breathing with respect to external influences, the dorsal respiratory group is to be considered.

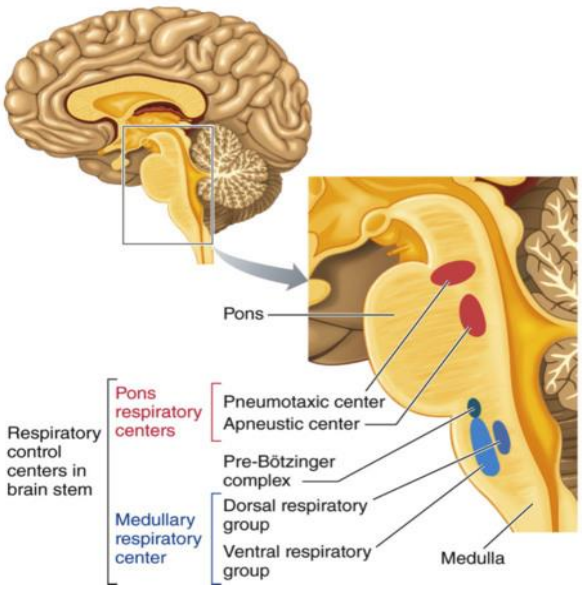
Pneumotaxic Area

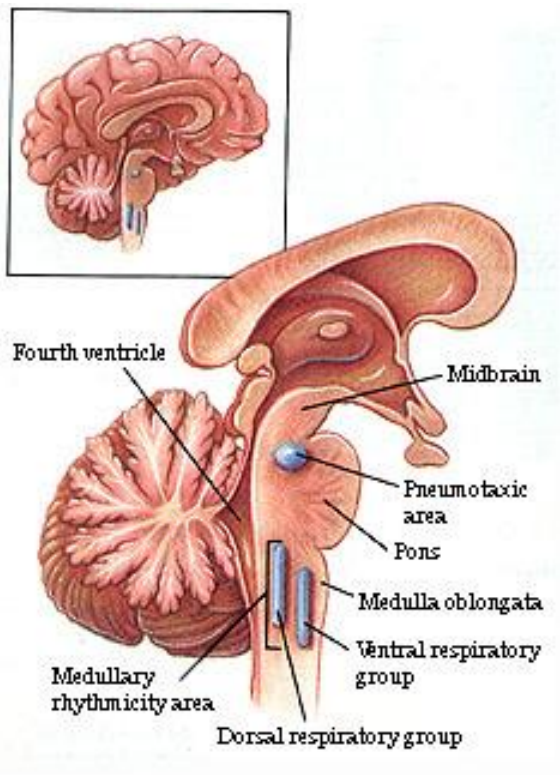
The pneumotaxic area, located in the upper pons, plays a crucial role in coordinating the transition between inhalation and exhalation. It transmits inhibitory impulses to the inspiratory area, helping to turn off the inspiratory area before the lungs become too full of air. By shortening the duration of inhalation, the pneumotaxic area ensures that the breathing rate can be adjusted. When this area is more active, it increases the breathing rate by reducing the time spent in inhalation.

Apneustic Area

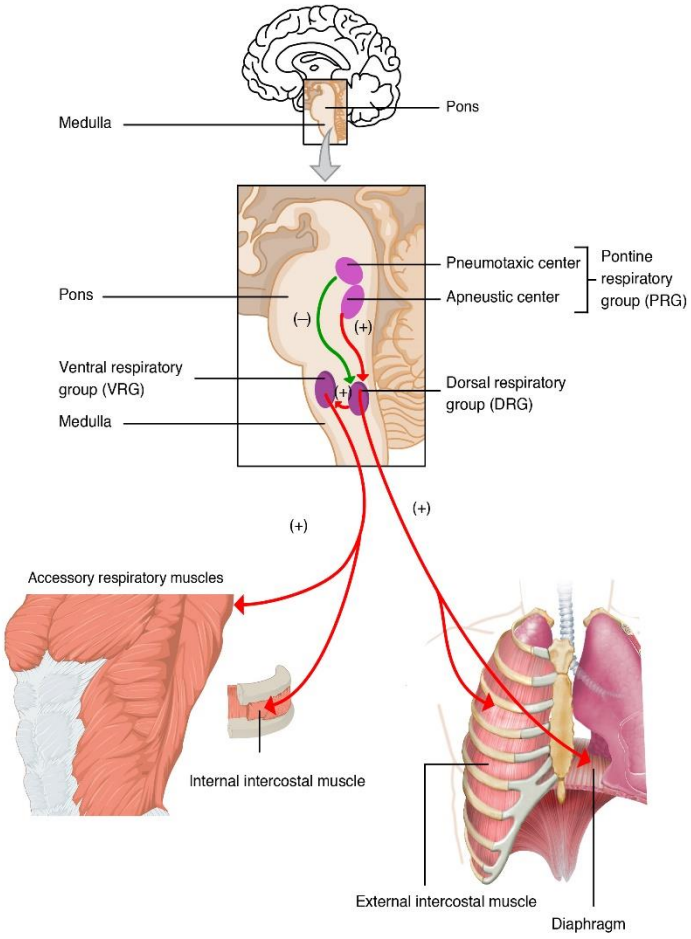
The apneustic area, located in the lower pons, also contributes to the regulation of breathing. It sends stimulatory impulses to the inspiratory area, prolonging inhalation and resulting in a long, deep breath. However, when the pneumotaxic area is active, it overrides the apneustic signals, preventing excessive prolongation of inhalation and maintaining a balanced breathing rhythm.







The respiratory centres



Anatomy of respiratory centres

The process of control

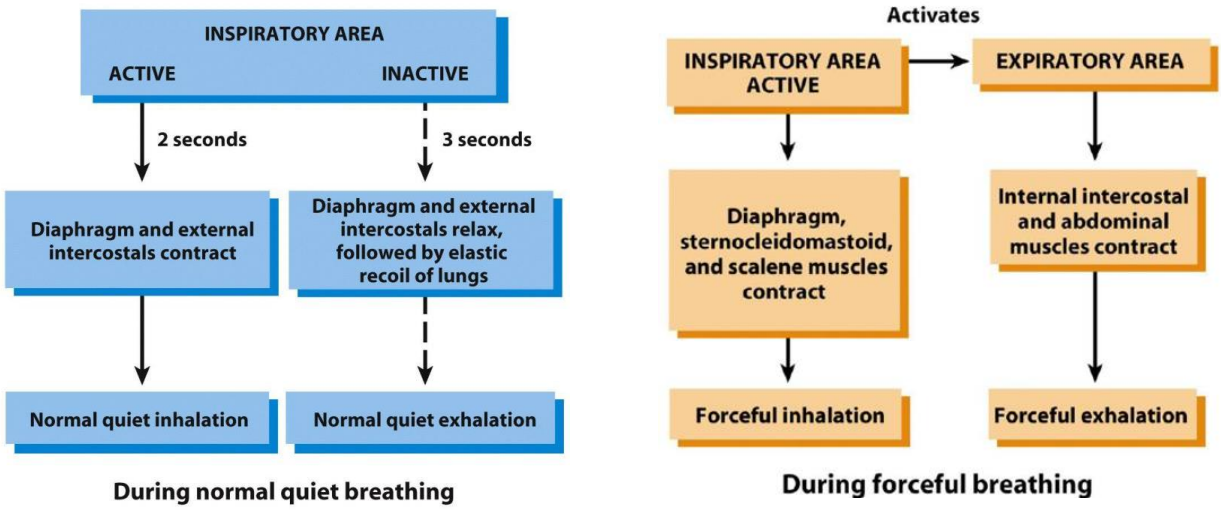
During normal quiet breathing, the inspiratory area (dorsal respiratory group) generates nerve impulses for about 2 seconds, causing the diaphragm and external intercostal muscles to contract. These impulses travel via the thoracic nerves (intercostal and subcostal nerves) to the external intercostal muscles of the rib cage and abdomen, and via the phrenic nerves to the diaphragm. As a result, the diaphragm and external intercostal muscles contract, leading to inhalation. During inspiration, the lungs inflate, and as they do, stretch receptors (proprioceptors) located in the bronchial tree are stimulated. These receptors send increasing numbers of nerve impulses via the vagus nerve to the expiratory centre, which temporarily inhibits the inspiratory centre, halting further inhalation.

Once the inspiratory area becomes inactive, nerve impulses cease, and the muscles relax for about 3 seconds, allowing the lungs and thoracic wall to return to their original shape and size through passive elastic recoil, leading to exhalation.

Once expiration occurs, the bronchial tree is no longer stretched, and the stretch receptors are no longer stimulated. At this point, the expiratory centre becomes inactive, allowing the inspiratory centre to initiate the next cycle of breathing. The entire process is repeated rhythmically throughout life, establishing the basic rhythm of breathing.

The neurons of the expiratory area remain inactive during quiet breathing. However, during forceful breathing nerve impulses from the inspiratory area activate the expiratory area. Impulses from the expiratory area cause contraction of the internal intercostal and abdominal muscles, which greatly decreases the size of the thoracic cavity and causes forceful exhalation

The depth of the inhalation force largely depends on that of the exhalation force.



Figures: Roles of the medullary rhythmicity area in controlling (a) the basic rhythm of respiration and (b) forceful breathing

Regulation of the Respiratory Centre

The basic rhythm of respiration set by the inspiratory area can be modified by inputs from other brain regions, receptors in the peripheral nervous system, and other factors.

Control of the respiratory centres by the apneustic and pneumotaxic

The control of the respiratory centres involves the coordinated actions of the pneumotaxic and apneustic areas in the pons, which work together to regulate the rhythm and depth of breathing.

The **pneumotaxic area**, located in the upper pons, plays a key role in managing the transition between inhalation and exhalation. It sends inhibitory signals to the inspiratory area, effectively shortening the duration of inhalation. By doing so, it prevents the lungs from becoming overly inflated. When the pneumotaxic area is more active, it increases the breathing rate by reducing the time spent in inhalation, thus allowing for quicker, more frequent breaths. The pneumotaxic centre is also inhibited by impulses from the expiratory centre, meaning decline in expiration (increase in inspiration) lifts the inhibition allowing it to fire inhibitory impulses to the apneustic centre.

On the other hand, the **apneustic area**, found in the lower pons, supports the inspiratory area by sending stimulatory signals that prolong inhalation. This results in longer, deeper breaths. However, if the pneumotaxic area is active, it can override the apneustic area's influence, preventing the excessive extension of inhalation. This balance between the two areas ensures a stable and efficient breathing pattern, adjusting the rhythm and depth of breaths as needed.

Chemoreceptor Regulation of Respiration

Certain chemical stimuli modulate how quickly and how deeply we breathe. The respiratory system functions to maintain proper levels of CO_2 and O_2 and is very responsive to changes in the levels of these gases in body fluids. There exist cells that are responsive to chemicals, called chemoreceptors. Chemoreceptors in two locations are sensitive to and monitor levels of CO_2, H^+, and O_2 and provide input to the respiratory centre. Central chemoreceptors are located in or near the medulla oblongata in the central nervous system. They respond to changes in H^+ concentration or PCO_2, or both, in cerebrospinal fluid. Peripheral chemoreceptors are located in the aortic bodies, clusters of chemoreceptors located in the wall of the arch of the aorta, and in the carotid bodies, which are oval nodules in the wall of the left and right common carotid arteries where they divide into the internal and external carotid arteries. (The chemoreceptors of the aortic bodies are located close to the aortic baroreceptors, and the carotid bodies are located close to the carotid sinus baroreceptors). Axons of sensory neurones from the aortic bodies are part of the vagus (X) nerves, and those from the carotid bodies are part of the right and left glossopharyngeal (IX) nerves.

Because CO_2 is lipid-soluble, it easily diffuses into cells where in the presence of carbonic anhydrase, it combines with water, to form carbonic acid. Carbonic acid quickly breaks down into H^- and HCO_3^- ions. Thus, an increase in CO_2 in the blood causes an increase in H^+ inside

cells, and a decrease in CO_2 causes a decrease in H^+. Normally, the PCO_2 in arterial blood is **40 mmHg**. If even a slight increase in PCO_2 occurs, a condition called hypercapnia or hypercarbia, the central chemoreceptors are stimulated and respond vigorously to the resulting increase in H^+ level. The peripheral chemoreceptors also are stimulated by both the high PCO_2 and the rise in H^+. In addition, the peripheral chemoreceptors (but not the central chemoreceptors) respond to a deficiency of O_2. When PO_2 in arterial blood falls from a normal level of 100 mmHg but is still above 50 mmHg, the peripheral chemoreceptors are stimulated. Severe deficiency of O_2 depresses activity of the central chemoreceptors and inspiratory area, which then do not respond well to any inputs and send fewer impulses to the muscles of inhalation. As the breathing rate decreases or breathing ceases altogether, PO_2 falls lower and lower, establishing a positive feedback cycle with a possibly fatal result. The chemoreceptors participate in a negative feedback system that regulates the levels of CO_2, O_2, and H^+ in the blood. As a result of increased PCO_2, decreased pH (increased H^+), or decreased PO_2, input from the central and peripheral chemoreceptors causes the inspiratory area to become highly active, and the rate and depth of breathing increase. Rapid and deep breathing, called hyperventilation, allows the inhalation of more O_2 and exhalation of more CO_2 until PCO_2 and H^+ are lowered back to normal. If arterial PCO_2 is lower than 40 mmHg, a condition called hypocapnia or hypocarbia, the central and peripheral chemoreceptors are not stimulated, and stimulatory impulses are not sent to the inspiratory area. As a result, the area sets its own moderate pace until CO_2 accumulates and the PCO_2 rises to 40 mmHg. The inspiratory centre is more strongly stimulated when PCO_2 is rising above normal than when PO_2 is falling below normal. As a result, people who hyperventilate voluntarily and cause hypocapnia can hold their breath for an unusually long period. Swimmers were once encouraged to hyperventilate just before diving in to compete. However, this practice is risky because the O_2 level may fall dangerously low and cause fainting before the PCO_2 rises high enough to stimulate inhalation. If you faint on land, you may suffer bumps and bruises, but if you faint in the water you could drown.

Cortical Influences on Respiration

The cerebral cortex has connections with the respiratory centre, allowing voluntary control over breathing patterns. For example, one can choose to hold our breath or alter our breathing rate consciously. This voluntary control is protective, enabling us to prevent water or irritating gases from entering the lungs. However, this control is limited by the body's need to maintain appropriate levels of carbon dioxide (CO_2) and hydrogen ions (H^+). When CO_2 and H^+ concentrations increase to a certain level, the inspiratory area is strongly stimulated, and nerve impulses are sent along the phrenic and intercostal nerves to the inspiratory (external intercostal) muscles, causing breathing to resume involuntarily.

In scenarios where someone holds their breath until they faint, the body's automatic control systems will take over, and breathing will resume once consciousness is lost. Additionally, nerve impulses from the hypothalamus and limbic system (for emotions, motivation, memory and olfactory) can influence the respiratory centre, allowing emotional states to affect respiration, such as during laughing or crying.

In summary, the respiratory centre in the brainstem, which includes the medullary rhythmicity area, pneumotaxic area, and apneustic area, controls the rhythm and depth of breathing. This system is finely tuned by both involuntary mechanisms and voluntary inputs from the cerebral cortex, ensuring that breathing is adjusted according to the body's needs and environmental conditions.

Feedback mechanism in response to oxygen deprivation.

The feedback mechanism in response to oxygen deprivation is crucial for maintaining homeostasis by ensuring adequate oxygen supply to tissues.

When oxygen levels drop, peripheral chemoreceptors in the carotid and aortic bodies detect this change and signal the respiratory centres in the brainstem via glossopharyngeal and vagus nerves to increase the rate and depth of breathing. This heightened respiratory activity, or hyperventilation, enhances oxygen intake and carbon dioxide expulsion, thereby restoring normal oxygen levels.

Central chemoreceptors, which respond primarily to elevated carbon dioxide levels and changes in pH, also contribute by stimulating the respiratory centres, indirectly supporting oxygen regulation. As oxygen levels normalize, the feedback loop reduces respiratory drive, stabilizing breathing. This mechanism protects against hypoxia by quickly correcting low oxygen levels and ensuring that tissues receive the oxygen needed to sustain vital functions.

Physiological changes during exercise

During exercise, the body undergoes several physiological changes to meet the increased demands for energy, oxygen, and nutrient delivery, while also managing the byproducts of heightened/elevated metabolic activity. Here's an overview of the key changes:

1. *Cardiovascular System*

- Increased Heart Rate: To pump more blood to the muscles, the heart rate increases. This is a direct response to the body's demand for more oxygen and nutrients.
- Vasodilation: Blood vessels, particularly those supplying the working muscles, dilate to increase blood flow, while vessels to non-essential organs constrict (vasoconstriction) to redirect blood to where it's most needed.

2. *Respiratory System*

- Increased Breathing Rate and Depth: To meet the elevated oxygen demands and to expel excess carbon dioxide, both the rate and depth of breathing increase, resulting in a higher minute ventilation (the total volume of air inhaled and exhaled per minute).

3. *Muscular System*

- Increased Blood Flow to Muscles: Active muscles receive a greater blood supply to deliver more oxygen and nutrients and to remove waste products like carbon dioxide and lactic acid.
- Increased Oxygen Utilization: Muscles extract more oxygen from the blood due to an increased capillary density and enhanced function of the mitochondria (the energy-producing organelles in cells).
- Lactate Production: During intense exercise, the body may rely more on anaerobic metabolism, leading to the production of lactic acid. The body increases its ability to buffer and clear lactate, delaying the onset of muscle fatigue.

4. *Metabolic Changes*

- Increased Energy Expenditure: The body ramps up the metabolism to meet the energy demands, utilizing glycogen stores in muscles and liver, and increasingly relying on fat stores as exercise continues.
- Thermoregulation: To dissipate the heat generated by increased metabolic activity, the body enhances sweat production and increases blood flow to the skin to cool the body through evaporative cooling.

5. *Hormonal Changes*

- Adrenaline and Noradrenaline Release: These hormones increase heart rate, blood pressure, and glucose availability, preparing the body for sustained physical activity.
- Insulin Sensitivity: Exercise enhances the muscles' sensitivity to insulin, facilitating glucose uptake and utilization for energy.
- Endorphin Release: The body releases endorphins, which can reduce the perception of pain and lead to a sense of well-being, commonly referred to as the "runner's high."

Physiological changes that occur at high altitude

At high altitude, the body undergoes several physiological changes to adapt to the reduced availability of oxygen, a condition known as hypoxia. These changes help the body maintain oxygen delivery to tissues despite the lower oxygen levels in the environment. Here's an overview of the key physiological changes:

1. Respiratory System

- Increased Breathing Rate (Hyperventilation): The body responds to lower oxygen levels by increasing the rate and depth of breathing to enhance oxygen intake and improve oxygen saturation in the blood.
- Respiratory Alkalosis: Hyperventilation leads to the excessive expulsion of carbon dioxide, causing a rise in blood pH (alkalosis). The kidneys gradually compensate by excreting bicarbonate to stabilize pH levels.

2. Cardiovascular System

- Increased Heart Rate: The heart pumps faster to deliver more oxygenated blood to tissues, compensating for the reduced oxygen content in each breath.
- Increased Cardiac Output: Initially, cardiac output rises due to the increased heart rate, helping to maintain oxygen delivery to vital organs and muscles.

3. Haematological Changes

- Increased Red Blood Cell Production (Erythropoiesis): The kidneys release more erythropoietin (EPO), a hormone that stimulates the production of red blood cells in the bone marrow. This increases the blood's oxygen-carrying capacity over days to weeks. Higher red blood cell counts leads to increased hemoglobin levels, allowing more oxygen to be transported per unit of blood.

4. Vascular System

- Increased Capillary Density: Over time, there is an increase in the density of capillaries in muscle tissue, improving oxygen delivery to cells.

5. Metabolic Changes

- Shift to Anaerobic Metabolism: At high altitude, the body may rely more on anaerobic pathways for energy production, especially during physical exertion, due to the reduced oxygen availability.
- Increased Production of 2,3-Bisphosphoglycerate (2,3-BPG): This molecule, found in red blood cells, increases in concentration at high altitude, promoting the release of oxygen from hemoglobin to tissues.

6. Fluid and Electrolyte Balance

- Diuresis: The body may excrete more fluid in response to the initial respiratory alkalosis, leading to increased urine production and potential dehydration.
- Fluid Redistribution: There may be a shift in fluid balance, with more fluid moving out of blood vessels into tissues, which can contribute to altitude-related oedema, such as high-altitude pulmonary oedema/edema (HAPE) or cerebral oedema (HACE).

7. Neurological Changes

- Hypoxic Symptoms: Initial exposure to high altitude can cause symptoms such as headaches, dizziness, and nausea due to the brain's sensitivity to reduced oxygen levels.
- Acclimatization: Over time, the brain adjusts to the lower oxygen levels, reducing these symptoms as part of the acclimatization process.

9. Sleep Patterns

- Disrupted Sleep: High altitude can lead to periodic breathing, where breathing cycles between rapid breathing and pauses, disrupting sleep and potentially leading to altitude-related insomnia.

These physiological changes occur as part of the body's adaptation to the low-oxygen environment at high altitudes, enabling individuals to function despite the challenging conditions. Acclimatization involves a gradual adjustment process, allowing the body to optimize oxygen utilization and maintain homeostasis over time.