Physiological control of respiration

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Introduction

Respiration involves the inward and outward movement of air into the lungs. This process facilitates gaseous exchange. The rate of respiration therefore regulates the partial pressures of oxygen (PaO₂) and carbon dioxide (PaCO₂) in the blood. Spontaneous respiration occurs as a result of rhythmic discharge of motor neurons innervating respiratory muscles. Nerve impulses from the brain are responsible for this rhythmic discharge. The rhythmic contraction and relaxation of respiratory muscles alternately fill the lungs during inspiration and empty them in expiration. This rhythmic discharges from the brain are regulated by changes in arterial PaO₂, PaCO₂ and hydrogen ion (H⁺) concentration, which is called the chemical control of respiration. A number of non-chemical influences also supplement the chemical control of respiration.

Regulation of respiration

Respiration is controlled through neuronal feedback loops, as illustrated in Figure 1. These feedback loops are comprised of the control centre, sensors, and effectors, namely:

- Control centre: the respiratory nuclei in the cerebral cortex and brainstem.
- Sensors: mechanoreceptors, and peripheral and central chemoreceptors.
- Effectors: muscles of respiration.

Neural control of respiration

The cerebral cortex, medulla and pons comprise the neural control of respiration. The cerebral cortex is responsible for voluntary control of breathing whereas the medulla and pons are responsible for automatic breathing. The nerve impulses arising from respiratory neurons in these areas regulate the activity of respiratory muscles, by activating motor neurons in the cervical and thoracic spinal cord that eventually innervate respiratory muscles. Therefore, the rate and depth of breathing is controlled by the input from these areas. The physical changes in the lungs are then sensed by the mechanoreceptors and central and peripheral chemoreceptors to further adjust the breathing.

Control of respiration from the higher brain centre (cerebral cortex)

The higher centre of the brain responsible for control of respiration is the cerebral cortex. It is responsible for voluntary control of respiration. The primary motor cortex is responsible for initiating any voluntary muscular movement, including that responsible for respiration. This function is achieved through signals that are sent to the spinal cord via corticospinal tracts and subsequently to the diaphragm and accessory muscles of respiration.

The superior portion of the primary motor cortex is responsible for initiating the voluntary contraction and relaxation of the internal and external intercostal muscles. Diaphragm control from the higher centre is also located within the superior portion
of the motor cortex posterior to the centre for thoracic control. Controlled exhalation is regulated from the inferior portion of the primary motor cortex.5

The cortex contains pathways for voluntary control that bypass medullary neurons. These pathways terminate in the motor neurons innervating the respiratory muscles.2 Voluntary thoughts can override all the other inputs to the respiratory centre4 and automatic control of respiration can sometimes be disrupted without loss of voluntary control, as the two systems are separate.2 However, voluntary control of respiration, such as breath-holding (inhibition of respiration), cannot occur indefinitely, because the chemoreceptor stimulation by hypoxaemia and/or hypercapnia overrides voluntary control.4 This point at which the inhibition of breathing can no longer voluntarily occur is called the breaking point.2,4

Respiratory control centre

The respiratory centre is comprised of four main anatomical areas, namely: the dorsal respiratory group (DRG) and the ventral respiratory group (VRG) located in the medulla, as well as the apneustic centre and the pneumotaxic centre which are located in the pons and are collectively called the pontine respiratory group (PRG),4 as shown in Figure 2.

Figure 2: Respiratory control centres in the pons and medulla6
**Medullary respiratory centres**

The medulla is the area of brain responsible for the respiratory pattern generation and where coordination of various voluntary and involuntary demands on respiratory activity occurs. The medullary respiratory centre is composed of two groups of neurons that are concentrated in two anatomical areas: the inspiratory centre (dorsal respiratory group) and the expiratory centre (ventral respiratory group).6,7

The DRG is located next to the nucleus tractus solitarius,7 near the root of cranial nerve IX.6 It has sensory afferents from peripheral chemoreceptors via the glossopharyngeal nerve and vagus nerve. Motor output is sent to the diaphragm from this centre via the phrenic nerve. This group of neurons primarily control the timing of the respiratory cycle.7 The DRG functions in both quiet or forced respiration and contains neurons that control lower motor neurons innervating the external intercostal muscles and the diaphragm.6

The VRG is a network of neurons located ventrally in the brain stem extending from the spinal cord to the pons-medulla junction.8 The VRG expiratory centre is primarily responsible for expiration.7 Its neurons innervate lower motor neurons controlling accessory respiratory muscles involved in active exhalation.6 These neurons are primarily inactive during quiet breathing because expiration is normally a passive process.7 The VRG inspiratory centre contains neurons involved in activities that involve maximal inhalation, such as gasping. There is reciprocal inhibition between the neurons involved with inhalation and exhalation, meaning that when inspiratory neurons are active, the expiratory neurons are inhibited, and vice versa.6

The VRG comprises the following respiratory neurons:

- Caudal ventral respiratory group which is mainly responsible for expiratory functions and comprises upper motor neurones passing to the contralateral expiratory muscles.
- Rostral ventral respiratory group which is involved in airway dilator functions of the larynx, pharynx and tongue.
- Pre-Bötzinger complex, responsible for central pattern generation.
- Bötzinger complex which has widespread expiratory functions.7

A cyclic interaction between the DRG and the VRG contributes to the basic pattern of respiration. For example, during forced breathing, the level of activity in the DRG stimulates neurons of the VRG that activate the accessory muscles involved in inhalation. Active exhalation follows each inhalation and takes place as the neurons of the expiratory centre stimulate the appropriate accessory muscles. The rate and rhythm of respiration cannot be attributed to a single area, even though the timing of this interaction is highly variable.6

**Pontine respiratory group (PRG)**

The apneustic and the pneumotaxic centres are neurons in the pons responsible for the modification of rhythmic discharges from the medullary neurons.6,7 They regulate the depth and rate of respiration in response to sensory stimuli or input from other centres in the brain.6

The pneumotaxic centre located in the upper pons interacts with the medullary respiratory centre (dorsal respiratory group) to reduce the depth of inspiration, thereby modulating the respiratory pattern.4 An increase in pneumotaxic output increases the rate of respiration by shortening the duration of each inhalation. A decrease in pneumotaxic output reduces the respiratory rate but increases the depth of respiration, because the apneustic centres will be more active in that instance.6

The apneustic centre is located in the lower part of the pons.4 On each side of the brain stem, the apneustic centre provides continuous stimulation to the DRG. During quiet breathing, stimulation from the apneustic centre helps increase the intensity of inhalation and normally after two seconds the apneustic centre is inhibited by signals from the pneumotaxic centre.6 During forced breathing, the apneustic centres respond to sensory input from the vagus nerves regarding the amount of lung inflation6 and prevent overexpansion of the lungs by modifying the dorsal respiratory group neurons.4

**Afferent input to the respiratory centre**

There are various inputs to the respiratory centre that are responsible for the regulation of respiration. The major inputs are the chemoreceptors (termed chemical control of respiration), as well as several non-chemical inputs.4

**Chemical control of respiration**

Chemoreceptor control

Change in the chemical composition of arterial blood, such as a rise in PaCO₂ or H⁺, or a reduction in PaO₂, leads to an increase in the level of respiratory neuron activity.2 This change in chemical composition stimulates chemoreceptors and a feedback of such a change is one way through which respiration is controlled. There are two types of respiratory chemoreceptors, namely:

- peripheral, and
- central chemoreceptors.

Both these types work in a slightly different way, but together they assist the body to control pH, PaO₂, and PaCO₂ in the blood,2 as shown in Figure 3.

**Peripheral chemoreceptors**

Peripheral chemoreceptors are the main influencer of respiration. These chemoreceptors are also termed arterial chemoreceptors and are located in the carotid (at the bifurcation of the carotid artery) and aortic bodies (on the aortic arch). The afferent impulses from the carotid bodies are carried via the
glossopharyngeal nerve, whereas those from the aortic bodies are carried via the vagus nerve. They detect chemical changes in the blood; for example, if they detect a drop in oxygen, decrease in blood pH (high H⁺) and an increase in PaCO₂, this will stimulate the chemoreceptors to stimulate the respiratory centre to increase the respiratory rate. This will then increase PaO₂, neutralise the pH and clear out PaCO₂.

The aortic and carotid bodies are the only chemoreceptors in the body that respond to hypoxaemia. High PaCO₂ stimulates both aortic and carotid bodies, however, the peripheral chemoreceptors are only responsible for 20% of the body’s response to hypercapnia. Low pH only stimulates the carotid bodies. Low blood pressure leads to hypoperfusion of the carotid and aortic bodies, subsequently increasing their neuronal output.

Central chemoreceptors

These chemoreceptors are located in the medulla, on the ventral surface, however, separate from the VRG. They detect chemical changes in the medulla. Central chemoreceptors are stimulated by a drop in cerebrospinal fluid (CSF) pH. Charged ions such as H⁺ and HCO₃⁻ cannot cross the blood–brain barrier, therefore for these ions to reach the central chemoreceptors a variety of events have to occur. Carbon dioxide (CO₂) diffuses from the blood into the CSF and then to the area surrounding the central chemoreceptors. CO₂ then reacts with water, catalysed by carbonic anhydrase (CA) enzyme to form carbonic acid (H₂CO₃) which then dissociates into H⁺ and HCO₃⁻. H⁺ then diffuses into the chemoreceptor tissue stimulating the chemoreceptors to activate the respiratory centre and thereby increasing respiratory rate.

Non-chemical control of respiration

Mechanoreceptors

Mechanoreceptors stimulate the respiratory centre through the lung stretch receptors and muscle spindles. The lung stretch receptors are located in the bronchial smooth muscle and they are stimulated by overinflation of the lung. The neural impulse from these receptors travels to the apneustic centre via the vagus nerve and results in a reduction in the depth of breathing. This reflex is called the Hering–Breuer inflation reflex. The Hering–Breuer inflation reflex occurs when the steady lung inflation results in an increase in the duration of expiration, whereas, a decrease in the duration of expiration as a result of marked lung deflation is called the Hering–Breuer deflation reflex.

Muscle spindles

During exercise there is a change in respiration and this change is initiated by muscle spindle activity. Impulses generated from afferent pathways of proprioceptors located in muscles, tendons, and joints stimulate inspiratory neurons during exercise and they in turn stimulate the respiratory centre to increase the respiratory rate, to help clear the carbon dioxide and acid produced by exercise and increase oxygen.

Irritant receptors

These receptors are located in the airway epithelium. They cause bronchoconstriction and stimulate ventilation as a protective mechanism in response to inhalation of noxious gases. Chemicals such as histamine also stimulate these receptors, thereby, activating rapidly adapting receptors in the trachea causing coughing, bronchoconstriction and secretion of mucus.

Juxtacapillary receptors (J-receptors)

These receptors are non-myelinated C-fibres in the alveolar walls and located in close proximity to pulmonary vessels, hence the name J (juxtacapillary) receptors. They are activated by hyperinflation of the lung, dyspnoea, bradycardia and hypotension. Intravenous or intracardiac administration of capsaicin also leads to the activation of these receptors, producing a reflex response termed pulmonary chemoreflex, which is characterised by apnoea, followed by rapid breathing.
bradycardia, and hypotension. This response is similar to the Bezold–Jarisch reflex produced by receptors in the heart. Although the physiological role of the pulmonary chemoreflex is unclear, it is believed to occur in pathologic states such as pulmonary congestion or embolisation.

**Pain receptors**

Ventilation is stimulated by activation of pain receptors. Hyperventilation during acute pain has been proposed to reflect the respiratory component of the fight-or-flight response, preparing the body for a possible attack or injury.

**Thalamus**

Ventilation is stimulated by an increase in core temperature. A study conducted in rats showed that increases in body temperature improve the mechanical properties of the respiratory system, such as increasing respiratory system compliance and decreasing airway resistance.

**Limbic system**

The fact that pain and emotional stimuli result in hyperventilation, suggests that afferents from the limbic system and hypothalamus send signals to the respiratory neurons in the brainstem.

**Conclusion**

Respiratory control involves multiple levels of regulation, including the higher, medullary and pontine centres, which provides regulatory activities that occur outside of our awareness. Chemicals such as oxygen, carbon dioxide and hydrogen ions affect breathing patterns through activation of respiratory chemoreceptors. In addition to the chemical afferent inputs to the respiratory centre, there are also non-chemical inputs that regulate respiration.

**Conflict of interest**

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**References**