

Respiration: control of ventilation

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Abstract

Rhythmic ventilation is an automatic process controlled by the central nervous system. Groups of cells in the brainstem, predominantly the ventral and dorsal respiratory groups, are responsible for generating basic respiratory rhythm. This basic rhythm is subject to modulation by both conscious and reflex actions. In normal individuals the respiratory minute volume is set to closely regulate arterial carbon dioxide tension (PaCO_2) at approximately 5.3 kPa, predominantly via a negative feedback reflex involving the central chemoreceptors. A separate group of chemoreceptors, the arterial chemoreceptors, are responsible for initiating the increased ventilatory response to counter arterial hypoxia, but a brisk response is not seen until PaO_2 levels fall to approximately 8.0 kPa from the normal 13.3 kPa. Combined hypercarbia and hypoxia (asphyxia) is a very powerful stimulus to breathe as the two inputs interact in a synergistic manner. The chemoreceptor reflexes can be modified when the need arises (e.g. blockade of the respiratory part of the arterial chemoreflex by the trigeminal reflex as part of the diving response). Other reflexes such as the Hering–Breuer reflex contribute to setting the balance between tidal volume and respiratory rate to attain a given minute volume, although this reflex does not appear to play a major role in humans at resting tidal volumes. Superimposed on this ‘tonic’ control, additional protective reflexes (e.g. from receptors in the upper airways) are recruited to protect the lungs and airways with responses such as coughs and sneezes when required.

Keywords Aortic bodies; arterial chemoreceptors; carotid bodies; central chemoreceptors; diving response; Hering–Breuer reflex; respiratory rhythm

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Ventilation is an automatic process that is controlled by the central nervous system. The brainstem is a key area responsible for the basic respiratory rhythm. This in turn is modulated by a number of influences ranging from conscious alterations (originating from ‘higher centres’), tonic reflexes such as the chemoreceptor reflexes regulating carbon dioxide levels of the blood and preventing dangerous hypoxia to episodic reflexes such as coughing and sneezing.

Origin of respiratory rhythm

The search for the area(s) of the brain and underlying mechanisms responsible for setting the basic respiratory rhythm has

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Learning objectives

After reading this article you should be able to describe the:

- neural arrangement that produces the basic respiratory rhythm
- short-term control of blood carbon dioxide, oxygen, pH and combined changes of these variables
- role of the peripheral chemoreceptors in controlling these variables, and of the central chemoreceptors when chronic hypoxia is present (at altitude)
- role of neural influences in regulating the chemoreceptor reflexes, as well as in regulating the rate and depth of ventilation

taken many years and is still continuing. Earlier ideas, based on experiments where gross changes in patterns of breathing were seen following transections and focal lesions in the brainstem led to the concept of multiple respiratory ‘centres’ (e.g. apneustic and pneumotaxic centres), which interacted to provide respiratory rhythm. This type of concept is now outdated and the altered pattern of breathing seen in these experiments is now viewed as the result of general damage rather than disconnecting specific centres.

Control of ventilation is affected by clusters of neurones that are grouped in several distinct areas of the brainstem. Two such areas in the medulla are called the ventral respiratory group (VRG) and the dorsal respiratory group (DRG). Current thinking is that rhythm generation is the domain of a group of tightly clustered neurones in the VRG (specifically in the rostral ventrolateral medulla) called the pre-Botzinger complex (PBC). Although the PBC is itself a complex area containing a heterogeneous population of neurones, the PBC neurones thought to be responsible for respiratory rhythmogenesis are all interneurones in the sense that they have no axons projecting out of the brainstem. PBC neurones then ‘drive’ groups of inspiratory neurones. A strong piece of evidence suggesting that the PBC neurones are indeed the respiratory rhythm generator is the finding that a small focal lesion in this area produces an immediate fatal apnoea. In addition, the VRG is viewed as being more important than the DRG in the generation of respiratory rhythm because the DRG has not been found in a number of species. The inspiratory neurones have a major output into the spinal cord and relevant cranial nuclei to influence the activity of relevant motoneurones. Other areas in the brain that influence the VRG (and DRG) are thought to modify the pattern of breathing, especially depth. One of these areas is the apneustic centre or Botzinger complex (Kolliker-fuse area) of the pons. Experimental evidence suggests that disruption of any of these areas (other than the PBC) will modify the depth or pattern of breathing, but will not abolish rhythmogenesis.

Control of carbon dioxide tension in arterial blood

Carbon dioxide tension in arterial blood (PaCO_2) is very closely regulated around a set point (5.3 kPa or 40 mmHg in a healthy individual) by a negative feedback system. A rise in PaCO_2 stimulates a reflex increase in ventilation, excreting excess CO_2 and returning PaCO_2 to the set point. Conversely, a fall in CO_2 attenuates tonic respiratory drive, resulting in a fall in ventilation

and accumulation of CO_2 until PaCO_2 has again reached normal levels (Figure 1). It is important to control PaCO_2 within such narrow limits because any alteration in PaCO_2 will in turn modify pH: hypercapnia causes a respiratory acidosis while hypocapnia causes a respiratory alkalosis. Significant changes in extracellular pH can lead to conformational changes in proteins such as enzymes and hence gross disturbances of body function.

The primary mechanism responsible for controlling PaCO_2 is a reflex originating from the central chemoreceptors. These chemoreceptors comprise a group of cells in the medulla of the brainstem, near the floor of the fourth cerebral ventricle (Figure 1b). The central chemoreceptors are separate and distinct from the cells generating respiratory rhythm, but the central chemoreceptors do normally provide a tonic respiratory 'drive'.

The predominant view is that the central chemoreceptors respond primarily to hydrogen ions (H^+) rather than directly to CO_2 . In this scheme the CO_2 in the cerebrospinal fluid (CSF) leads to the generation of H^+ (Figure 1b) and stimulation of the chemoreceptors. Because the CSF contains few buffering proteins a change in CO_2 levels here causes greater alterations in H^+ levels than in the blood. Since CO_2 can cross the blood–brain barrier with ease, any change in blood CO_2 is fairly quickly reflected by an alteration in CSF CO_2 , and ultimately a change in chemoreceptor activity. Although the same reaction (resulting in elevation of H^+ levels when CO_2 levels rise) takes place in the blood,

the resulting H^+ in the blood is irrelevant for the central chemoreceptors because H^+ cannot diffuse across the blood–brain barrier in healthy individuals.

Having given the detailed description of the response of the central chemoreceptors to extracellular CSF H^+ , it should be noted that some authors take a different view and argue that the central chemoreceptors respond to a change in intracellular H^+ levels resulting from an alteration in extracellular CSF CO_2 levels.

Control of oxygen tension in arterial blood

Oxygen tension in arterial blood (PaO_2) is also controlled by a negative feedback reflex. However, PaO_2 is not regulated as sensitively as PaCO_2 until there has been a considerable fall in PaO_2 from the normal levels of approximately 13.3 kPa to about 8.0 kPa, beyond which there is a powerful increase in ventilation. Increases in PaO_2 above 13.3 kPa have little effect on ventilation (Figure 2), presumably because humans have not evolved with a threat of hyperbaric oxygen. One reason why this sort of control is appropriate for oxygen relates to the oxyhaemoglobin dissociation curve. Most of the oxygen in normal blood is bound to haemoglobin; hence, it is the amount and degree of saturation of haemoglobin that dictates the amount of oxygen carried in blood (CaO_2). The oxyhaemoglobin dissociation curve is sigmoidal (Figure 2). At normal arterial oxygen tensions haemoglobin is about 98.5% saturated and we are on the upper flat part of the curve. Consequently, falls in PaO_2 to about 8.0 kPa have relatively little effect on CaO_2 . However, falls below this level results in our descent down the steep part of the oxyhaemoglobin curve and consequently large, dangerous, falls in CaO_2 . Hence, the need for a strong stimulus to breathing is only necessary if PaO_2 falls below approximately 8.0 kPa.

The receptors responsible for monitoring arterial oxygen tension are the peripheral or arterial chemoreceptors found in the carotid and aortic bodies. These organs receive an enormous blood flow in relation to their mass of tissue. Estimations of the total carotid body blood flow range from 700 to 2000 ml/minute/100 g, which far exceeds the organ's metabolic demand and hence the venous effluent from the carotid bodies normally have arterial-like oxygen levels. The situation is likely to be similar in the aortic bodies. As a consequence of this high blood flow the tissue derives all of the oxygen needed for metabolic purposes from the plasma rather than needing to extract oxygen from haemoglobin. As a result they effectively monitor the tension of oxygen in plasma (PaO_2) rather than the content of oxygen in arterial blood (CaO_2). Normally, this arrangement is adequate to monitor blood oxygen levels since the concentration of functional haemoglobin does not usually vary acutely. However, in circumstances where functional haemoglobin levels do drop (e.g. anaemia or carbon monoxide poisoning) CaO_2 can drop to dangerously low levels without detection by the arterial chemoreceptors.

The arterial chemoreceptors are sensitive to alterations in their blood flow. This is probably the reason why significant haemorrhage quickly leads to increased ventilation as an intense sympathetically-derived vasoconstriction in the arterial chemoreceptors, coupled in severe haemorrhage with reduced arterial blood pressure, causes a marked reduction in chemoreceptor blood flow and hence stagnant hypoxia locally in the chemoreceptors.

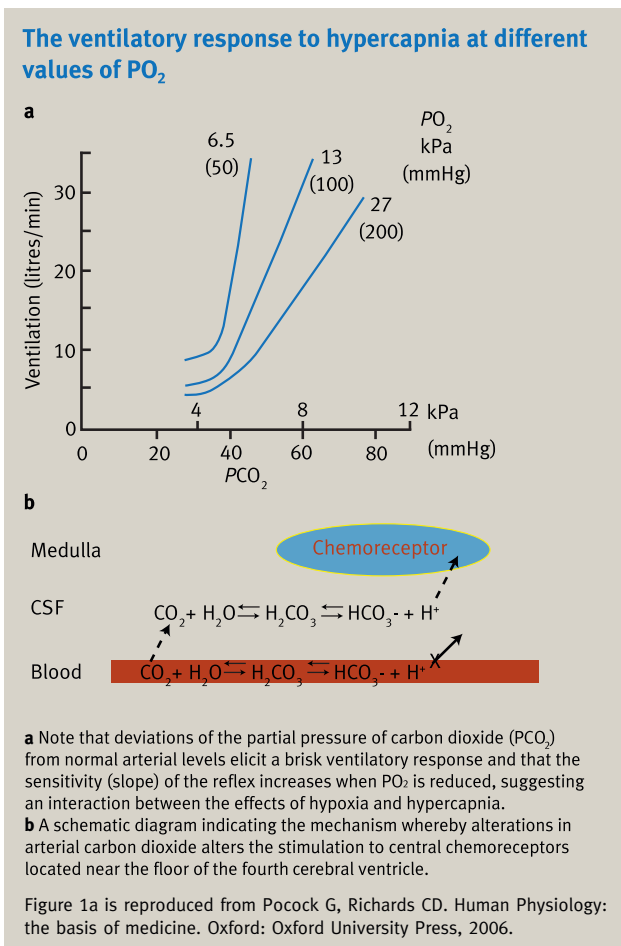


Figure 1

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