Physiology in Clinical Neurosciences
Brain and Spinal Cord Crosstalks
Hemanshu Prabhakar *Series Editor*

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Brain and Lung Crosstalk

Springer

Physiology in Clinical Neurosciences – Brain and Spinal Cord Crosstalks

Series Editor

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Central nervous system that includes brain and spinal cord has high metabolic demand. The physiology of the brain is such that it is easily affected by any altered physiology of other systems which in turn may compromise cerebral blood flow and oxygenation. Together the brain and spinal cord control our body systems to function automatically. While other systems of body controls individual functions, central nervous system at the same time does many different functions, especially, controlling the function of other systems. However, only little is known that central nervous system itself affects almost all the other systems of the body for example, cardiovascular, respiratory, renal, genitourinary, gastrointestinal, hematological etc. This interaction of brain and spinal cord with other systems makes it important for us to understand how any kind of injury to the central nervous system may at times, produce complications in remote organs or systems of the body. It is these lesser known crosstalks between acutely or chronically affected brain and spinal cord and other systems of the body that is discussed in this book series. Each system would be considered in a separate book.

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To our parents, our families, and our teachers

Hemanshu Prabhakar
Charu Mahajan

Preface

Central nervous system that includes the brain and spinal cord has a high metabolic demand. The physiology of the brain is such that it is easily affected by any altered physiology of other systems which in turn may compromise cerebral blood flow and oxygenation. Together the brain and spinal cord control our body systems to function automatically. While other systems of body controls individual functions, central nervous system at the same time does many different functions, especially, controlling the function of other systems. However, only little is known that central nervous system itself affects almost all the other systems of the body, for example, cardiovascular, respiratory, renal, genitourinary, gastrointestinal, and hematological. This interaction of the brain and spinal cord with other systems makes it important for us to understand how any kind of injury to the central nervous system may at times produce complications in remote organs or systems of the body. It is these lesser known *cross talks* between acutely or chronically affected the brain and spinal cord and other systems of the body that is discussed in this book series. We plan to bring out a series of seven books and each body system would be considered in a separate book.

The first in the series discusses the brain–respiratory system physiology and the brain–lung cross talk. The pathophysiology of the lung injury following the brain injury has been discussed in detail in this book. During clinical management, the conflicts between the brain and lungs in relation to the tidal volumes, positive end-expiratory pressures, arterial carbon dioxide and oxygen levels, recruitments maneuvers, and positioning has been closely explained. The possible future therapeutic targets have also been explored by the contributors.

We are grateful to the contributors who believed in the proposed format of the work. We are sure the readers would be benefited by the cognizance of the renowned experts. The purpose of this opuscule will be truly accomplished if we are able to improve the clinical conditions of our patients by providing better care.

New Delhi, India Hemanshu Prabhakar
New Delhi, India Charu Mahajan

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Neurophysiology of Respiratory System

1

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Contents

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1.1 Introduction

We are born with our first breath and die with our last. In between the two events, breathing continues uninterrupted without us being consciously aware of it unless it becomes laboured due to extreme physiological demands or in disease states. This chapter focuses on the neural substrate and the mechanisms that controls breathing at rest and modulates breathing with changing physiological demands and behavioural states.

The evolution of respiratory and cardiovascular system coincides with the development of multicellular organism for a unifying purpose of providing oxygen to cells and eliminating carbon dioxide in proportion to the energy demands of the organism. The essential design feature of the respiratory and cardiovascular system is the sequential transport of gases, to and fro between the external environment and all the cells of the body. The respiratory system provides a means for external convection for movement of the air between the external environment and alveolar exchange zone (respiratory membrane) where diffusion of oxygen and carbon dioxide occurs between air and blood (Fig. 1.1). The cardiovascular system provides a means for internal convection for the movement of blood between the respiratory exchange zone and cells of the body. Ventilation (achieved by respiratory system) and perfusion (achieved by cardiovascular system) are synchronized not only at organ level (minute ventilation and cardiac output) but also at alveolar level. Synchronization is also achieved within the depth and phase (inspiration–expiration) of ventilation, heart rate and stroke volume. At operational level, the rate of delivery of ambient air into the alveolar exchange region is matched with perfusion through the capillaries of pulmonary circulation to fulfil homeostatic requirements of the organism. For efficient transport of gases, the respiratory and cardiovascular

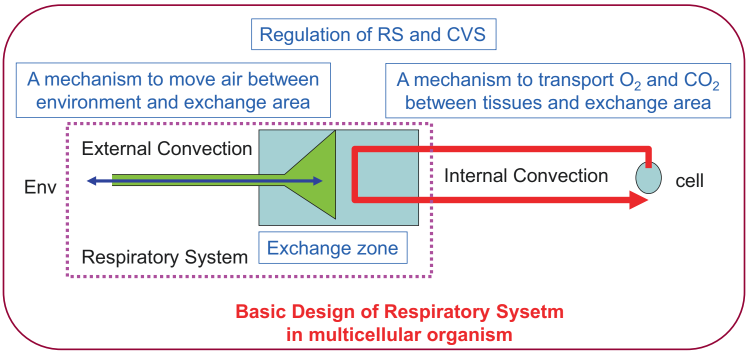

Fig. 1.1 Basic design of respiratory system. Gases are transferred between ambient air and cells of the body, sequentially through respiratory and cardiovascular system. The ventilatory mechanism moves the gases between the ambient air and alveoli. The cardiovascular system moves the blood carrying gases between alveoli and cells. Each system has its control mechanism to synchronize with each other for efficient gaseous transfer

system are not only coupled in time and space but also controlled concurrently and coherently.

Apart from its primary ventilatory function, over the course of evolution, the respiratory system has become integrated with many other motor behaviours (Holstege 2014). Alteration in ventilation occurs in different states of sleep and arousal, anxiety (hyperventilation), aggression, fear (breath-holding), feeding and mating (sniffing), defence (hyperinflation) and laughing. Increase in intra-thoracic pressure and intra-abdominal pressure is required during vocalization, speech, vomiting, parturition, mating and locomotor activities. Apart from this, the respiratory system has its own protective reflexes such as coughing and sneezing. Synchronization of phases of respiration with deglutition is important to prevent inadvertent aspiration. Additionally, the respiratory system plays a critical role in the acid–base balance, temperature regulation in panting animals and acts as pump for venous return. The pulmonary vasculature provides a low-pressure high conductance path for circulation of blood and is involved in the metabolism of biomolecules and trapping of emboli that originate in the peripheral venous circulation before they reach arterial circulation.

The huge of functions subserved by respiratory system requires an intricate network of core groups of respiratory neurons that integrate the afferent information coming from the lungs, chemoreceptors and muscles with information from higher centres relating to emotions, sleep–wake state, voluntary and involuntary motor behaviours.

The description of the neural network in subsequent sections has been organized into an initial brief historical commentary, description of phases of respiration followed by control of respiration covering basic design of network, organization of the neuronal groups, description of individual neuronal groups, afferents and neural networks underlying rhythmogenesis and pattern of different phases of respiration.

1.2 Historical Perspective

Experimental investigations for elucidating the neuronal centres for control of respiration began in the nineteenth century. Later, investigations expanded to identification of chemical factors and mechanisms for respiratory modulation. By mid-nineteenth century, the primacy of medulla in neural control of respiration was established and, in the early twentieth century, network of specialized respiratory centres in ponto-medullary regions of the brainstem were identified. By 1930s, it was established that partial pressures of CO_2, O_2 and concentration of H^+ in blood, and the concentration of H^+ in the cerebrospinal fluid modified ventilation through respiratory centres in brainstem. Various reflexes originating in specialized peripheral chemoreceptors in carotid and aortic bodies, and mechanoreceptors from the lung parenchyma were also characterized (Gesell 1939; Bernthal 1944).

The relative role of peripheral (carotid and aortic bodies) and central chemoreceptors and mechanisms underlying ventilatory response to hypercapnia, hypoxia and acidity were elucidated in this period (Gesell 1925). These developments were best utilized by Henderson, a physiologist, who embarked on using a mixture of oxygen and carbon dioxide for inhalation at the end of anaesthesia and for resuscitation of asphyxic patient due to varied causes and changed the practice of medicine (Henderson and Turner 1941). The exercise hyperpnoea was found to be less related to partial pressure of CO_2 and O_2 in the blood and more driven by afferents originating from exercising muscles (Comroe 1944).

Multiple factor theory of control of ventilation was put forth by John Gray in 1946 to replace then prevalent theory of unique chemical factor for primary control of ventilation (Gray 1946). It was proposed that there are multiple factors that act independently and simultaneously but not independent of each other to influence ventilation and these factors include concentration of O_2, CO_2, H^+ in blood, proprioceptor receptors from muscles, pressure receptors in great arteries and veins, thermoreceptors (hypothalamic), pain and psychogenic reflexes. In both physiological and pathological conditions, change in one of the factors tends to affect other factors either directly or as a response to change in the initiating factor.

The mechanism underlying genesis of respiratory rhythm was not resolved and both pacemaker automaticity and reflexive mechanisms were considered (with inspiratory and expiratory centres). Theoretical models of respiratory system as feed-back regulator of CO_2 in blood were published (Grodins et al. 1954) and mathematical models were generated (Grodins et al. 1967).

The most favoured model was based on Lumsden's experiments where a tonically active apneustic centre provided the primary inspiratory drive that was patterned for rate, depth and rhythm by pneumotaxic centre and reflexive inputs from peripheral chemoreceptors and lung parenchyma (Lumsden 1923a; Lumsden 1923b). With increasing anatomical resolution of ablation and stimulation studies, localized aggregates of neurons in medulla were named as inspiratory and expiratory centres based on their properties. By 1960s, three regions of medulla namely, a dorsal respiratory group (DRG) associated with nucleus tractus solitarius (NTS), and two ventrolateral respiratory groups (VRG) around nucleus ambiguus and nucleus retroambigualis were recognized. Further studies led to DRG being recognized as the primary integrator of the sensory information for sniffing and Hering–Breuer reflex. The VRG was shown to have rostral inspiratory group and caudal expiratory group of respiratory neurons.

By 1970s, it was widely accepted that respiratory rhythm is generated in medulla. However, due to lack of definitive evidence, both the pacemaker theory where a group of neuronal cells with intrinsic rhythmogenic property and network theory based on interaction between groups of neuron without intrinsic rhythmogenic properties were considered as plausible (Mitchell and Berger 1975).

In 1991, an intrinsically and spontaneously rhythmogenic group of neurons were identified in Pre-Botzinger Complex (Pre BotC) of the ventrolateral medulla (Smith et al. 1991). Since then, major advances have been made in our understanding of the intricate neural network for control of respiration. Distinct neuronal groups in the ponto-medullary regions have been characterized on molecular and physiological basis and details of their interconnectivity have been worked out. These will be discussed in Sect. 1.5.

1.3 Phases of Respiration

Respiration is a cyclic event and each phase of respiration is controlled by distinct neuronal groups. Traditionally, the cycle of respiration is described as consisting of two phases viz. inspiration and expiration. However, on the basis of the firing pattern of respiratory neurons in the brainstem, premotor and motor neurons of respiratory muscles (phrenic, hypoglossal, vagal), the respiratory cycle is divided into three phases: inspiration (I), post-inspiration (PI or E1) and expiration (E2) (Richter 1982; Smith et al. 2013) (Fig. 1.2). These phases of respiratory cycle are driven by neuronal groups in pons, medulla and spinal cord. These neurons are classified according to their firing pattern and temporal relationship with the three phases of respiration (Smith et al. 2013).

Inspiratory phase Inspiratory phase is characterized by ramp activity in the phrenic nerve and is accompanied with incremental activity of hypoglossal and vagus nerves. The activity in hypoglossal nerve and vagus precedes the activity in the phrenic nerve leading to reduction in airway pressure even before the movement of air due to decrease in intrathoracic pressure caused by phrenic nerve. During raised inspiratory effort, activity in nerves supplying accessory inspiratory muscles also occurs.

Post-inspiratory phase (PI) This phase is characterized by a sharp decline in activity in phrenic and hypoglossal nerves with increase in activity in the vagus nerve. The activity in phrenic nerve and hypoglossal nerves declines quickly in the initial one-third of the post-inspiratory phase, while the vagal activity declines slowly over the whole of post-inspiratory phase extending slightly into the expiratory phase. A small residual activity in phrenic (crural diaphragm) and strong activity in vagus (laryngeal adductors) during this phase applies a 'brake' on expiration. The increase in upper airway resistance and prevention of sudden relaxation of

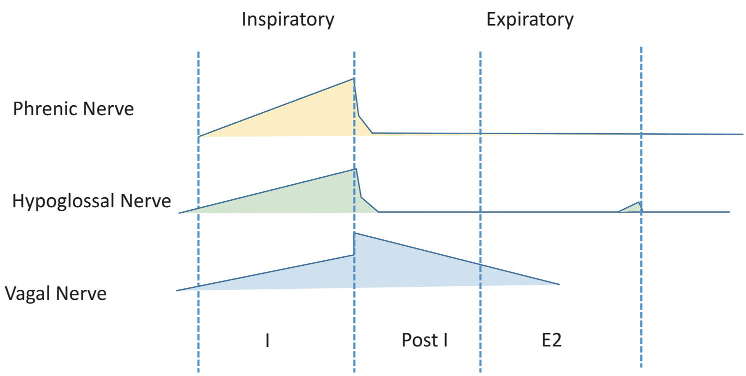

Fig. 1.2 Phases of respiration: The three phases of respiration namely inspiratory, post-inspiratory and expiratory are distinguished on the basis of the activity of the nerves and muscles supplied by them *(adapted from Smith 2013)*