Review Article

Respiratory rhythm generation

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In the past ten years considerable progress has been made in understanding the neural system which produces the rhythm of respiration. So much so, that textbooks of physiology have had difficulty in remaining current. It is therefore the object of this review to present the information and ideas currently available in this field of research. The presentation method used here is tutorial in manner. While references are made to the main body of scientific literature, there has been no attempt to produce an exhaustive listing. In a similar spirit, discussion of methodologies involved has been kept to a minimum. By these means, it is hoped to provide an informative and interesting view of this fascinating physiological system.

For those interested in a more detailed review of the scientific literature on the subject, the reviews by Long and Duffin¹ as well as those by Richter² and von Euler³ are recommended.

The rhythmic drive to respiratory motoneurons in the spinal cord originates from neurons in the brainstem. It appears to be unlikely that the groups of respiratory neurons in the medulla are inherently rhythmic, pacemaker cells,⁴ and so current theory favours the idea that these neurons are connected so as to form an oscillator. How such an oscillator is formed is as yet not understood, but a considerable knowledge of these cells and some of their interconnections has been gained. Most of the experimental work which seeks to elucidate such mechanisms has been done using electrophysiological methods in cats, and so, unless specified, the descriptions of

medullary anatomy which follow are for the cat. Figure 1a and 1b locate the anatomical reference point for the location of the medullary nuclei concerned with respiratory rhythm. It is the obex, the point at which the central canal widens to form the fourth ventricle. Several respiratory nuclei are located bilaterally near the obex, running longitudinally along the neuraxis.

Closest to the obex (see Figure 1b) is the nucleus tractus solitarius, and a group of respiratory neurons whose action potentials occur in a bursting pattern during inspiration are located in the ventrolateral part of this nucleus.⁵⁻⁹

Further lateral and ventral (see Figure 1b), the nucleus ambiguus contains vagal motoneurons which exhibit a variety of firing patterns with a respiratory rhythm.¹⁰⁻¹³ Just ventrolateral to the nucleus ambiguus lies the nucleus retroambiguus containing respiratory neurons whose activity occurs in several types of respiratory bursting patterns.^{13,14}

Since the vagal motoneurons of the nucleus ambiguus which innervate the larynx and pharynx are mostly silenced by deep pentobarbitone anaesthesia without interrupting spontaneous respiration,^{15,16} they have not been thought to be an essential part of the respiratory rhythm generator mechanism,¹⁷ and are therefore neglected in this presentation.

Thus, the respiratory neurons of interest are located in the medulla as shown in Figure 1b. Their action potentials occur in bursts synchronous with particular phases of respiration and this forms the basis of their nomenclature. Figure 2 illustrates several of the patterns of activity observed in these neurons.

Inspiration

The phrenic motoneurons and external intercostal motoneurons are driven to produce inspiration by medullary inspiratory neurons in both the ventrolateral

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FIGURE 1 Localization of the obex, the anatomical reference point for the coordinates of the medullary respiratory neurons in the cat. (a) An overall, rostrally directed view of the dorsolateral aspect of the cerebellum and medulla exposed by an occipital craniotomy. (b) A caudally directed view of the dorsolateral aspect of the isolated medulla with the cerebellum removed, the two main nuclei containing respiratory neurons with spinal axons; the population associated with the nucleus tractus solitarius, and that of the nucleus retroambiguus.

FIGURE 2 Patterns of activity recorded extracellularly from medullary respiratory neurons. Traces top to bottom are: (1) an inspiratory neuron of the ventrolateral nucleus tractus solitarius; (2) inspiratory neurons of the nucleus retroambiguus; (3) electromyogram of the diaphragm.

FIGURE 3 A sectional view of the medulla illustrating a typical axonal pathway for an inspiratory neuron of the ventrolateral nucleus tractus solitarius.

teral portion of the nucleus tractus solitarius and the nucleus retroambiguus. The axons of all of these cells cross the midline in the region just rostral to the obex and descend the contralateral spinal cord.

Figure 3 shows the path of an axon of a typical inspiratory cell of the nucleus tractus solitarius.^{7,8,13,18,19} These neurons have been demonstrated to drive phrenic motoneurons^{9,20-22} as well as descending to thoracic levels of the cord²³ to drive intercostal motoneurons. In addition to spinal projections, these neurons have ipsilateral, collateral projections to the nucleus retroambiguus.^{15,17,24}

Figure 4 shows typical axonal pathways for the inspiratory neurons of the rostral, nucleus retroambiguus. Approximately 25 per cent of the crossed axons arborize in the phrenic nucleus before continuing caudally to thoracic levels of the spinal cord,^{13,16} and these neurons have been demonstrated to drive phrenic motoneurons²² and external intercostal motoneurons.²⁰ In addition to spinal projections, these neurons have collateral projections to both the ipsilateral and contralateral nucleus retroambiguus although they do not appear to project to the nucleus tractus solitarius.¹⁵⁻¹⁷

FIGURE 4 A sectional view of the medulla, illustrating a typical axonal pathway for an inspiratory neuron of the rostral nucleus retroambigualis.

These medullary inspiratory neurons in the nucleus tractus solitarius and nucleus retroambigualis make up the pre-motor population, driving spinal inspiratory motoneurons to produce inflation of the lungs. As might be expected they are influenced by both pulmonary and chemoreceptor afferents, although few examples of such afferent connections have been actually demonstrated. Much of the evidence for such afferent connections is circumstantial. For example, elevated levels of carbon dioxide cause these inspiratory neurons to increase their firing frequency during their inspiratory burst. However, since the central chemoreceptors have not yet been conclusively identified, the afferent pathway remains unknown.

The evidence for peripheral chemoreceptor (carotid body) afferent input is stronger. Direct stimulation of the glossopharyngeal nerves has been shown to affect the inspiratory neurons of the nucleus retroambigualis and the nucleus tractus solitarius.²⁵ Both anatomical²⁶⁻³⁰ and electrophysiological^{28,31,32} studies have shown that afferent fibres of the carotid sinus nerve project to the nucleus tractus solitarius. This nucleus also receives afferents from facial and trigeminal nerves, aortic and superior laryngeal nerves, and vagus nerves.³³⁻³⁶

The pulmonary afferent information reaching these two populations of inspiratory neurons can be roughly classified into two types; irregular to

bursting action potentials from irritant or rapidly adapting pulmonary receptors, and regularly occurring action potentials whose frequency of firing reflects lung volume from pulmonary stretch receptors.

Hyperventilation of the lungs above normal tidal volume causes medullary inspiratory neurons to react with a high frequency burst of action potentials,^{7,8,37} and produces a "gasp" inspiratory effort (Head's paradoxical reflex). Because the irritant type of pulmonary receptors are also activated strongly³⁸⁻⁴⁰ by the hyperinflation, it has been assumed that the pulmonary irritant receptors excite the bulbospinal inspiratory neurons.

Pulmonary stretch receptors, on the other hand, produce action potentials at a rate proportional to lung volume,^{39,40} and a moderate lung inflation acts to shorten the burst of inspiratory neuron action potentials^{6,41,42} thereby halting inspiration (the Hering-Breuer inflation reflex). The inspiratory neurons of the nucleus tractus solitarius react in two different ways. The alpha type behaves like the inspiratory neurons of the nucleus retroambigualis in that the burst of action potentials is shortened in duration but otherwise unchanged. The beta type, however, shows an increased firing frequency before stopping, and can even be caused to produce a short burst of action potentials during expiration by a gentle inflation of the lungs. "Pump cells,"⁷ so called because they have a bursting rhythm in time

FIGURE 5 A sectional view of the medulla, illustrating a typical axonal pathway for an expiratory neuron of the caudal nucleus retroambigualis.

with the ventilation pump, are probably beta type neurons with an exaggerated response to pulmonary receptors engendered by preparations in which lung volume is particularly low.⁸ These stereotyped responses to lung inflation have been observed by many investigators.^{7,8,27,42-46}

As well as these coincidental observations, pulmonary afferents have been traced to the nucleus tractus solitarius,⁴⁷⁻⁵¹ but such direct evidence is not available for the inspiratory neurons of the nucleus retroambigualis.

Expiration

Although expiration is mostly a passive process, nevertheless, during increased ventilatory drive, expiration may become active. In this case the expiratory motoneurons in the thoracic levels of the spinal cord innervating internal intercostal and abdominal muscles are driven by medullary expiratory neurons.

There are two medullary populations of expiratory neurons; one in the caudal (below the obex) portion of the nucleus retroambigualis, and the other in a region at the rostral end of the nucleus retroambigualis, which has been named the Böttinger complex. However, the purpose served by each of these populations appears to be quite different. The caudal nucleus retroambigualis expiratory neurons provide the drive to expiratory muscles but the Böttinger

expiratory neurons act to inhibit inspiratory elements during the expiratory period.

Figure 5 shows the path of an axon of a typical expiratory neuron of the caudal nucleus retroambigualis. These neurons have been shown to have axons descending the contralateral cord to thoracic levels^{13,16,52} arborizing extensively from T2 to L3²² and, although direct excitation of internal intercostal motoneurons has been demonstrated,⁵³ the influence of these medullary expiratory neurons on spinal expiratory motoneurons is likely to be via spinal interneurons.⁵⁴

The expiratory neurons of the caudal nucleus retroambigualis are influenced by both carbon dioxide and pulmonary afferents. They show an increased firing frequency during their burst activity when carbon dioxide levels are elevated⁵⁵⁻⁵⁹ and respond to lung inflations. The expiratory neuron response to lung inflation may be mixed, depending on the strength of activation of irritant and stretch receptor populations. Low volume lung inflations produce a lengthened burst of higher frequency activity, but higher volume inflations may produce inhibition as well.⁶⁰ These observations have been interpreted to imply that expiratory neurons of the caudal nucleus retroambigualis are excited by pulmonary stretch receptors and inhibited by pulmonary irritant receptors.

Figure 6 shows the path of an axon of a typical ex-

FIGURE 6 A sectional view of the medulla, illustrating typical axonal pathways for expiratory neurons of the Bötzinger complex.

piratory of the Bötzinger complex. These expiratory neurons, only recently discovered,⁶¹ have extensive bilateral collaterals among both medullary nuclei^{22,62,63} as well as sending axons down the contralateral cord.^{63,64} They have been demonstrated to be inhibitory to the inspiratory neurons of the nucleus tractus solitarius⁶² and to the phrenic motoneurons. So far, little has been learned about the afferent inputs to the Bötzinger expiratory neurons. Their response to lung inflations appears to be similar to that of the expiratory neurons of the caudal nucleus retroambiguus.^{22,60,65}

The Bötzinger expiratory cells provide an explanation for the expiratory phase inhibition of phrenic motoneurons and medullary inspiratory neurons, which prior to their discovery had been assigned to the expiratory neurons of the caudal nucleus retroambiguus by default, despite evidence to the contrary that such expiratory neurons had no medullary collaterals^{15,16,22} and did not inhibit phrenic motoneurons.²²

Interneurons

The medullary neurons discussed so far all have spinal axons, and are responsible for the patterning of activity in respiratory motoneurons. Hence, apart from modification by spinal mechanisms, these neurons determine ventilatory patterns. This leaves

the question as to how these medullary neurons are patterned themselves.

Within the rostral portion of the nucleus retroambiguus (above the obex) a number of respiratory interneurons have been found. One of these, termed the early-burst inspiratory type^{13,16,18} has a bursting pattern of activity which begins at the start of the inspiratory phase at a high firing frequency and then tapers off to quiescence about halfway through the inspiratory phase. Figure 7 shows that the axons of these cells cross the mid-line and arborize in the contralateral nucleus retroambiguus.^{15-17,22}

The function of the early-burst inspiratory interneurons has been inferred from indirect evidence to be inhibitory; preventing the firing of expiratory neurons in the nucleus retroambiguus during inspiration and retarding the firing of inspiratory neurons in the nucleus retroambiguus for the first part of inspiration so that the firing pattern is one of gradually increasing firing rate.^{15,16,66,67}

While the early-burst inspiratory interneuron has therefore been postulated to be a major determinant of the expiratory neuron firing pattern, the question remaining is how inspiration is terminated. Figure 7 shows the late-inspiratory interneuron postulated to be responsible.^{66,68-70} This interneuron has been found within the region of the nucleus ambiguus and nucleus retroambiguus, and has a firing

FIGURE 7 A sectional view of the medulla, illustrating typical locations and axonal connections for the early-burst inspiratory, late-inspiratory and postinspiratory types of interneurons.

pattern consistent with the arrival of inhibition to the inspiratory neurons.⁷¹ In turn, the late-inspiratory interneuron is postulated to be inhibited by the early-burst inspiratory neurons.⁷⁰

Recently it has been suggested that respiration should not be thought of as the alternation of two phases; inspiration and expiration, but rather as the sequencing of three phases; inspiration, postinspiration and expiration. This conception was prompted by several observations. If the pattern of phrenic activity is examined closely, there appears to be a graded increase of activity through inspiration until all activity abruptly ceases momentarily. Then the activity abruptly reappears, almost as strong as before the interruption, and rapidly declines to quiescence. After the quiescent period of the expiratory phase, the cycle repeats. The period of decaying activity after the momentary interruption and before the quiescent expiratory period has been termed the postinspiratory phase and is thought to perform a braking action on expiratory flow. It is interesting to note that expiratory neurons are not active during this postinspiratory period.

An interneuron has been found (Figure 7), within

the medullary region between the nucleus tractus solitarius and the nucleus retroambigualis, which has a pattern of activity synchronous with the postinspiratory phase.^{2,70,72} By inference, this interneuron is thought to excite the inspiratory neurons and possibly prevent expiratory neurons from beginning to fire.

Rhythm generation

With this last interneuron the list of known medullary respiratory neurons is complete. Figure 8 is a conglomerate of all of the previous sectional views and gives a very limited idea of the complexity of the system. Some of the types are only newly discovered and in many cases the interconnections postulated between these different types of neurons are inferred from circumstantial evidence rather than direct demonstration.

Despite the limited evidence, an idea of the oscillator can be obtained by considering both the connections which have been postulated and their effects. Figure 9 attempts to do this. While the figure does not explain rhythm generation it does provide a picture of the current state of knowledge and points up the gaps in it. The model assumes that respiration is made up of three phases; the inspiratory, postinspiratory and expiratory phases.

At least four populations of neurons determine the inspiratory phase. The early-burst inspiratory neurons are inhibitory to the bulbospinal inspiratory neurons of both the nucleus retroambigualis and nucleus tractus solitarius as well as to the late inspiratory interneurons, so that the bulbospinal inspiratory neurons have an incrementing frequency of firing during inspiration and the late inspiratory interneurons are prevented from firing until late in inspiration. The bulbospinal inspiratory interneurons driving the respiratory motoneurons are then inhibited by the late inspiratory interneurons and inspiration ceases. Throughout inspiration, the expiratory neurons of the nucleus retroambigualis, the Bötzing expiratory neurons and the postinspiratory interneurons are all presumed to be actively inhibited by the early-burst inspiratory neurons.

During the subsequent postinspiratory phase, the inspiratory bulbospinal neurons have a declining frequency of firing, matching and presumed to be caused by, the postinspiratory interneurons. Both the expiratory neurons of the nucleus retroambigualis

FIGURE 8 A sectional view of the medulla combining the previous views of the axonal pathways of the respiratory neurons.

and the Bötzing expiratory neurons are delayed in the onset of their firing, by as yet unknown mechanisms.

The final phase of the cycle, the expiratory phase, is characterized by an augmenting frequency of firing of the bulbospinal expiratory neurons in both the nucleus retroambiguus and Bötzing complex. Throughout this phase the inspiratory bulbospinal neurons are inhibited by the Bötzing expiratory neurons. The early-burst inspiratory neurons and the postinspiratory interneurons are also inhibited by unknown mechanisms. At the end of this phase, the expiratory neurons cease firing abruptly with the onset of firing of early-burst inspiratory neurons, and the cycle repeats itself.

The picture that is emerging is a great deal more complex than that of a decade ago. Then, the premotor respiratory neurons were thought to be interconnected to form an oscillator, and now, after the discovery of several more types of respiratory neurons, the site of respiratory rhythm generation appears to have moved back one step to the interneurons. Current theory explains the firing patterns of respiratory neurons as due to direct interactions between types. For example, the inspiratory neurons'

firing pattern of an increasing rate during the first half of inspiration is the result of the gradual withdrawal of inhibition by the early-burst inspiratory neurons. While such hypotheses are attractive they do not answer some of the fundamental questions which still remain.

One of the major difficulties in explaining rhythm generation has been the so-called millisecond to second gap, referring to the fact that action potentials occur at millisecond time scales whereas breathing is a process cycling over several seconds. How does one connect together fast neurons to create a slow oscillator?

Another basic question which has remained has been to explain how populations of neurons, whose behaviour in terms of activity pattern is similar, can all be co-ordinated to act together. In other words, what makes all of the inspiratory neurons synchronous on the respiratory time scale?

This latter question might be answered if it could be shown that the neurons were also synchronized on the millisecond time scale of neuronal events. Studies from our own laboratory^{9,73-75} have shown that there are indeed cases of synchronized firing of neurons which are near neighbours anatomically.

FIGURE 9 A diagram categorizing the medullary respiratory neurons according to their phase of activity and showing their interconnections schematically. See the text for a fuller explanation. (Reproduced¹ by permission of the authors and the Canadian Journal of Physiology and Pharmacology.)

However, such synchronization is weak, both in terms of its frequency of occurrence within a population, and its strength for pairs of neurons. Moreover, current techniques cannot discern whether such weak synchronization is due to drives common to the neurons or due to interconnections between the neurons.

Although the evidence has not yet been obtained,

the data so far do suggest a possible description of the system which may account for some of its fundamental characteristics. To speculate: a given population of, say, inspiratory neurons could be loosely connected via dendrodendritic or electronic synapses. Because such synaptic coupling leads to a sharing of potential among neurons coupled in this way, the population as a whole becomes both

FIGURE 10 The effect of increasing inspired concentrations of halothane on an inspiratory neurone of the rostral nucleus retroambigualis. Within each panel the top trace is the neuronal activity and the bottom trace is the massed phrenic nerve potential. A, control; B, after 10 min of 0.5% halothane; C, after 10 min of 1% halothane; D, after 10 min of 1.5% halothane; E, after 10 min of 2.0% halothane.

unified in its response to the drives of its individual members and also slow in its collective response. It is as though the population of individual neurons form a sort of super neuron, distributed in space, and slow because of its large membrane surface area.

Such a model would explain why all members of a population are synchronized on the long respiratory time scale but not on the short neuronal time scale, and also, why the response to any drive is relatively sluggish so that the firing pattern of inspiratory

neurons is a slow build up of firing frequency over the inspiratory burst.

To halt such a loosely coupled population abruptly at the end of inspiration requires a massive and synchronized, and therefore fast, inhibition of all members. Such a role could be fulfilled by the late inspiratory interneurons.

Thus, the respiratory oscillator could be thought of as a population of inspiratory cells whose membrane potentials are loosely coupled together so that the population acts together, but slowly, in

response to excitatory drives such as chemoreceptor input. When activity reaches a sufficient level, inhibition synchronously resets the entire population to a subthreshold level. The expiratory phase occurs while the inspiratory population remains below threshold, being slowly driven towards inspiratory activity by chemoreceptor inputs. Such a description of the respiratory oscillator is highly speculative, and perhaps this description is more appropriate for the respiratory interneurons than for the premotor populations.

One idea that has become more clearly established within the past decade has been the concept that respiratory rhythm is not so much an alternation between the equal and opposite activities of inspiration and expiration, but rather the breaking up of a constant inspiratory drive to allow expiration to take place periodically. Thus, the withdrawal of the chemical drive to breathe in sheep whose venous blood was circulated through a membrane lung to withdraw carbon dioxide at a rate equal to the metabolic production, resulted in a conscious, non-breathing sheep with normal arterial blood gases.⁷⁶

A further example more pertinent to anaesthesia may be given. Provided that the anaesthetic does not produce specific effects on peripheral inputs to the medullary respiratory oscillator, like the stimulation of pulmonary irritant receptors for example, then the effect of anaesthesia is to cause respiratory rhythm to fail, not because the inspiratory neurons fail to operate and drive spinal motoneurons, but because the oscillator fails to cycle properly into expiration. Figure 10 clearly shows this effect with increasing concentrations of halothane. The experiment was done in a cat initially anaesthetized with pentobarbitone (control). To reduce effects other than those of the anaesthetic halothane directly upon the medullary respiratory neurons, the vagi were cut bilaterally and the cat was paralysed with a succinylcholine infusion and ventilated to keep carbon dioxide level constant.

The bulbospinal inspiratory neuron, recorded in the nucleus retroambiguus (Figure 10, top trace), and the phrenic nerve massed potential (Figure 10, lower trace) both continue to be active during the inspiratory phase as the anaesthetic dose increases (Figure 10, A to E), but the inspiratory phase lengthens.

This experiment therefore illustrates two of the

points made in this review. First, the pathways from the chemoreceptor drives to the respiratory motoneurons are not markedly depressed by the anaesthetic. It is the cycling mechanism which fails to inhibit the inspiratory neurons and cycle the system into expiration. One interpretation, therefore, is that the cycling mechanism, the rhythm generator, is separate from the premotor, bulbospinal inspiratory neurons.

The second observation is that the crucial step in generating respiratory rhythm is to stop inspiration. The experiment shows little change taking place in the expiratory period as the anaesthetic dose increases. The drives which start inspiration are present but the mechanism which stops inspiration is failing. The overall model of the respiratory rhythm generator appears to be a periodic halting of inspiration to allow expiration to take place, rather than a bistable balance between equipotent inspiratory and expiratory populations.

These experimental observations, and their interpretation in the light of present hypotheses about the generation of respiratory rhythm, conclude this review. The past ten years have yielded much information about the interconnections between the medullary respiratory neurons, particularly those immediately premotor to the spinal motoneurons. However, the mechanism responsible for rhythm generation remains unknown, and attention has become focussed upon the respiratory interneuron populations of the medulla.

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