J. exp. Biol. (1982), 100, 93–107
With 11 *figures*
Printed in Great Britain

GENERATION AND MAINTENANCE OF THE RESPIRATORY RHYTHM

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SUMMARY

Activities of the phrenic and internal intercostal nerves show that the central nervous rhythm of respiration consists of 3 phases: inspiratory, postinspiratory and expiratory. The discharge patterns of medullary respiratory neurones of the anaesthetized, paralysed cat can be correlated with these phases of the central respiratory cycle, and the postsynaptic activity of individual cells can be analysed to obtain information about the populations of neurones converging upon them. Inferences are drawn about respiratory neurone connectivity and a theory is developed that the respiratory network primarily employs inspiratory-related neurones and that medullary expiratory neurones are less important for the rhythmogenesis of respiration. It is suggested that the inspiratory network consists of a ramp generating excitatory loop network of interneurones whose discharge is brought to an end ('off-switched') by inhibitory late-inspiratory interneurones. The discharge pattern of the latter type of neurone is explained by inhibition arriving from early-inspiratory interneurones. Subsequent to 'off-switching' the ramp generator is assumed to be immediately gated by a very powerful post-inspiratory inhibition whereas expiratory activity seems to be disfacilitated at this time. This is the period when 'passive' (stage 1) expiration occurs. Following this interposed postinspiratory phase 'active' (stage 2) expiration may begin, depending on the amount of excitatory inflow to the inspiratory ramp generator. When expiratory neurones are activated the inspiratory system is again synaptically inhibited and the frequency of ventilation is markedly slowed.

INTRODUCTION

The investigation of the respiratory behaviour of mammals is one of the most traditional fields in physiology. At the beginning of the last century a large number of scientists concentrated their interest on locating those central nervous structures which generate and control respiratory movements (Flourens, 1851; Legallois, 1812; Longet, 1847). Their work formed the basis for the concept of respiratory centres in the brainstem which was further developed by Lumsden (1923) in the classical model of interacting respiratory subcentres, i.e. pneumotaxic, apneustic and gasping centres in the pons and the medulla.

A large variety of new techniques have been developed and new data added since those days: extracellular recordings from single nerve cells have revealed the existence of spinal, medullary and pontine 'respiratory' neurones, i.e. cells discharging in synchrony with inspiration or expiration (Achard & Bucher, 1954; Andersen & Sears,

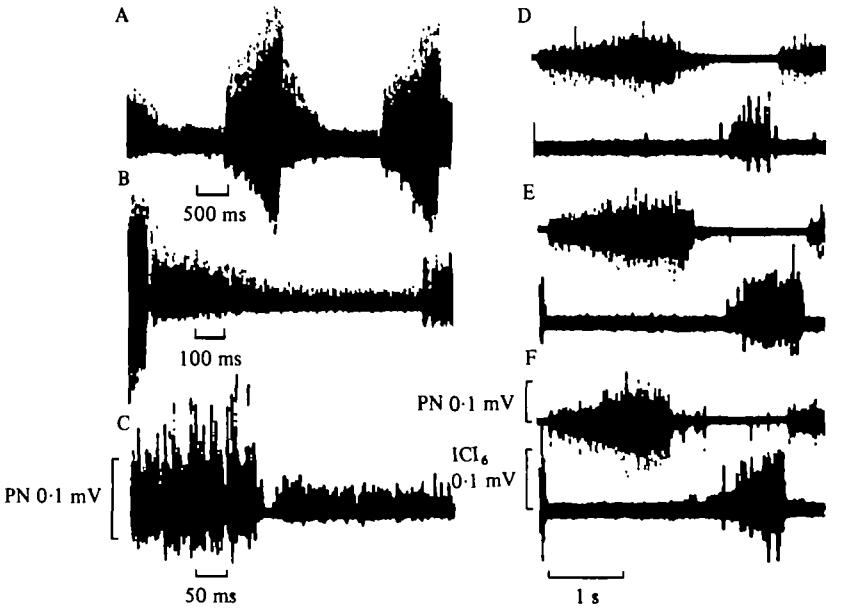

Fig. 1. Efferent discharges recorded from the phrenic nerve (PN) in A–F and the internal intercostal nerve of the sixth thoracic segment (ICI 6) in D–F of a chloralose anaesthetized cat.

1964; Batsel, 1964; Baumgarten, 1956; Cohen & Wang, 1959; Hoff & Breckenridge, 1949; Merrill, 1970, 1981; Salmoiraghi & Burns, 1960*a*; Sears, 1964*a*, *b*). Bulbospinal and bulbar interneurones have been identified using antidromic stimulation (Nakayama & Baumgarten, 1964), while microstimulation techniques have enabled single cell axons and some of their collateral branches to be traced to different areas of the brainstem and spinal cord (Merrill, 1974). The localization of retrogradely transported horseradish peroxidase has given us a picture of the pathways connecting those brain areas containing cell bodies of respiratory neurones (Kalia, 1977, 1981; Kalia, Feldman & Cohen, 1979). The positive cross-correlations between the firing of simultaneously recorded respiratory neurones has indicated the possibility of oligosynaptic interconnections (Cohen, 1976; Feldman, Sommer & Cohen, 1980; K. P. Madden, J. P. Baker and J. E. Remmers, in preparation). Further, intracellular recordings from respiratory neurones (Baumgarten, Balthasar & Koepchen, 1960; Hildebrandt, 1974; Mitchell & Herbert, 1974; Richter, Heyde & Gabriel, 1975; Salmoiraghi & Baumgarten, 1961) have enabled their postsynaptic activity to be analysed, revealing some of the variety of afferent inputs converging on respiratory neurones (Richter *et al.* 1979).

THE RESPIRATORY RHYTHM

The basic respiratory behaviour of anaesthetized animals is generally described by reference to phrenic or intercostal nerve activity. In the phrenic nerve a steadily increasing 'ramp' activity during inspiration (Fig. 1 A) is followed by a rapid decline and often by a short period of silence (Fig. 1 C). This in turn is followed by some

weaker activity which declines steadily (Fig. 1 B). The latter corresponds to the period when 'passive' expiration occurs, i.e. inspiratory muscles gradually relax, allowing the lungs to collapse slowly. Expiratory airflow does not occur passively during this period but is controlled by the resistive action of activated adductor muscles in the larynx (Gautier, Remmers & Bartlett, 1973; Harding, Johnson & McClelland, 1979). When inspiratory muscle contraction comes to an end expiratory alpha spinal motoneurones start to discharge (Fig. 1 D–F) and produce active expiratory movements. This period of 'active' expiration may fail, however, during quiet or rapid shallow breathing.

This behaviour of spinal respiratory motoneurones challenges the classical description of the 'central' (neuronal), respiratory rhythm as consisting of only two antagonistic nervous phases, i.e. central inspiration and central expiration. It implies the existence of a third, interposed phase. In this review this interposed phase of mainly passive expiration will be called 'stage 1' of expiration. Active expiration will be called 'stage 2' of expiration when ventilatory functions are described, but the term 'post-inspiratory', suggested by Gautier *et al.* (1973) will be used when nervous activities are discussed. The term post-inspiratory emphasizes that this activity does not seem to be a remnant of the preceding inspiratory discharge but represents a separate activity evidently playing an essential role in the central rhythmogenesis of respiration.

DISCHARGE PATTERNS OF MEDULLARY NEURONES

Lesion experiments have shown that there is a network of medullary neurones which can generate an automatic, though primitive rhythm (Lumsden, 1923; Breckenridge & Hoff, 1950; Gautier & Bertrand, 1975; Hukuhara, 1973; Ngai & Wang, 1957; Salmoraghi & Burns, 1960*b*; St John, Glasser & King, 1971, 1972; Tang, 1967 and Wang, Ngai & Frumin, 1957). This review is focused on medullary respiratory neurones of the cat but it must be emphasized that pontine (St John & Knuth, 1981) and spinal (Sears, 1964*a*) structures seem necessary to explain all aspects of automatic ventilation.

The respiratory neurones in the medulla consist of bulbospinal 'medullary output' neurones projecting to the spinal cord (Nakayama & Baumgarten, 1964), vagal motoneurones innervating laryngeal muscles (Gacek, 1975) and higher order, i.e. non-spinally projecting interneurones (Bianchi, 1971). The neurones can be identified as inspiratory or expiratory by correlating their discharge with the activity of the phrenic or intercostal nerves (Fig. 2).

In the lower brainstem, expiratory neurones, (i.e. neurones discharging an augmenting pattern of spikes between the bursts of phrenic nerve activity), seem to be functionally uniform (Merrill, 1974) regardless of whether they are medullary interneurones or bulbospinal neurones. In chloralose, halothane or nembutal anaesthetized cats the majority of these neurones do not start to discharge before phrenic activity comes to an end and stage 2 of expiration begins (Fig. 2 G). Some expiratory neurones, however, start to discharge at low and rather constant frequencies during the late period of stage 1 expiration (Fig. 2 F), increasing their discharge in an augmenting pattern only during stage 2 of expiration. Caudal expiratory neurones never start firing at the

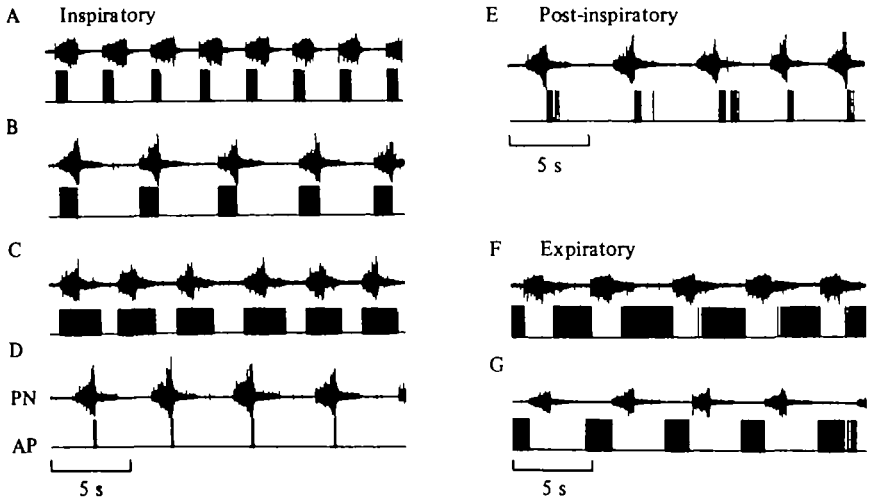

Fig. 2. Firing patterns of different types of respiratory neurone located in the medulla of pentobarbital anaesthetized cats. Neurones are classified as being inspiratory when they fire action potentials (AP) during the phrenic nerve discharge (PN), as postinspiratory when they fire only during stage 1 of expiration and as expiratory when they discharge predominantly during stage 2 of expiration.

very onset of stage 1 expiration and those expiratory medullary neurones which are present in more rostral brainstem areas seem to behave similarly (Lipski & Merrill, 1980; Merrill, 1970; 1981).

In contrast to expiratory neurones there is a large variety of discharge patterns among medullary inspiratory neurones. The majority of these neurones fire an augmenting pattern of spikes approximately in phase with the ramp component of phrenic nerve activity. Many of them stop firing after phrenic discharge has passed its peak (Fig. 2B) but some continue to fire at declining frequencies throughout the postinspiratory phase (Fig. 2C). This type of inspiratory neurone includes bulbospinal and medullary interneurones. The discharge is the same in 'beta' neurones, i.e. neurones receiving an excitatory synaptic input from lung stretch receptor afferents (Baumgarten & Kanzow, 1958), as in 'alpha' inspiratory neurones which lack such an input. An additional population of 'late' inspiratory neurones discharges only during the late period of the inspiratory ramp (Fig. 2D). This discharge reaches its maximum during the time when the inspiratory ramp comes to an end. Two types of neurone, firing in phase with phrenic nerve activity, have a declining discharge pattern: one type discharges during the early period of inspiration and has its maximum frequency at the very beginning of its activity (Fig. 2A). These 'early inspiratory' neurones regularly stop firing before the second third of inspiration. The other type is active only during the postinspiratory period and does not discharge during stage 2 of expiration (Fig. 2E). In this latter respect they obviously differ from the otherwise comparably reacting 'early expiratory' neurones described by Feldman & Cohen (1978). The onset of this postinspiratory discharge occurs rather abruptly as phrenic activity is decreased to postinspiratory levels.

This variety in the firing patterns of medullary respiratory neurones indicates that

various sorts of interaction occur within the population of inspiratory neurones and that the connectivity between expiratory neurones is more simply organized. It is also consistent with the view that the respiratory rhythm is generated primarily by inspiratory-related neurones (Bradley *et al.* 1975; Euler, 1980; Wyman, 1977) and that medullary expiratory neurones are less important for the rhythmogenesis of respiration.

PATTERNS OF POSTSYNAPTIC ACTIVITY OF INSPIRATORY NEURONES

At present there is no evidence for respiratory pacemaker activity, i.e. for endogenously rhythmic cells within the medulla. The respiratory rhythm, therefore, is assumed to arise from synaptic interactions within the network of respiratory neurones (Cohen, 1979, 1981; Wyman, 1977). To obtain information about these synaptic interactions, excitatory (e.p.s.p.s) and inhibitory (i.p.s.p.s) inputs to respiratory neurones have been analysed from intracellular recordings. Such analysis reveals the average discharge behaviour of whole populations of neurones converging on the individual respiratory cell in question and by correlating cell firing patterns with the postsynaptic activity of individual cells one may draw some inferences about respiratory neurone connectivities and develop some theories about the form of this network.

Typical inspiratory bulbospinal neurones and many of the higher order interneurones reveal a steadily decreasing membrane potential during inspiration which then turns to a steady increase during stage 1 and stage 2 of expiration (Fig. 3A). Some cells continue to discharge during stage 1 of expiration but never during stage 2. The analysis of their postsynaptic activity reveals that during inspiration alpha neurones receive an augmenting pattern of e.p.s.p.s which is abruptly shunted by i.p.s.p.s at the end of inspiration (Fig. 3B, D, F), the latter evidently arising close to the soma. These i.p.s.p.s arrive late in inspiration, their pattern is very steeply augmenting and they continue into the early period of postinspiratory activity in the phrenic nerve. This pattern of i.p.s.p.s resembles the pattern of spike discharge in late inspiratory neurones.

After this short-lasting inhibition comes to an end the input resistance of alpha neurones again increases (Fig. 3B, C) and under normal circumstances the membrane slowly starts to hyperpolarize during stage 1 of expiration (Fig. 3A). Inhibitory postsynaptic events, if present at all, seem to occur remotely on the dendritic tree of these neurones. Sometimes, however, when postinspiratory activity is absent from the phrenic nerve there is a prominent wave of i.p.s.p.s in these bulbospinal inspiratory neurones. Beta bulbospinal and some alpha and beta higher order interneurones reveal a similar input of inspiratory e.p.s.p.s but do not seem to receive a comparably strong late inspiratory inhibition. During the postinspiratory phase they show an interaction of e.p.s.p.s and i.p.s.p.s and the membrane potential is normally slowly hyperpolarized. Nevertheless, there is a significant decrease in their input resistance (Fig. 4B). After chloride ion injection two distinct waves of reversed i.p.s.p. patterns become evident, the first being correlated with the postinspiratory activity and the second with stage 2 of expiration (Fig. 4A).

The membrane behaviour of all the inspiratory cells again changes when stage 2 of

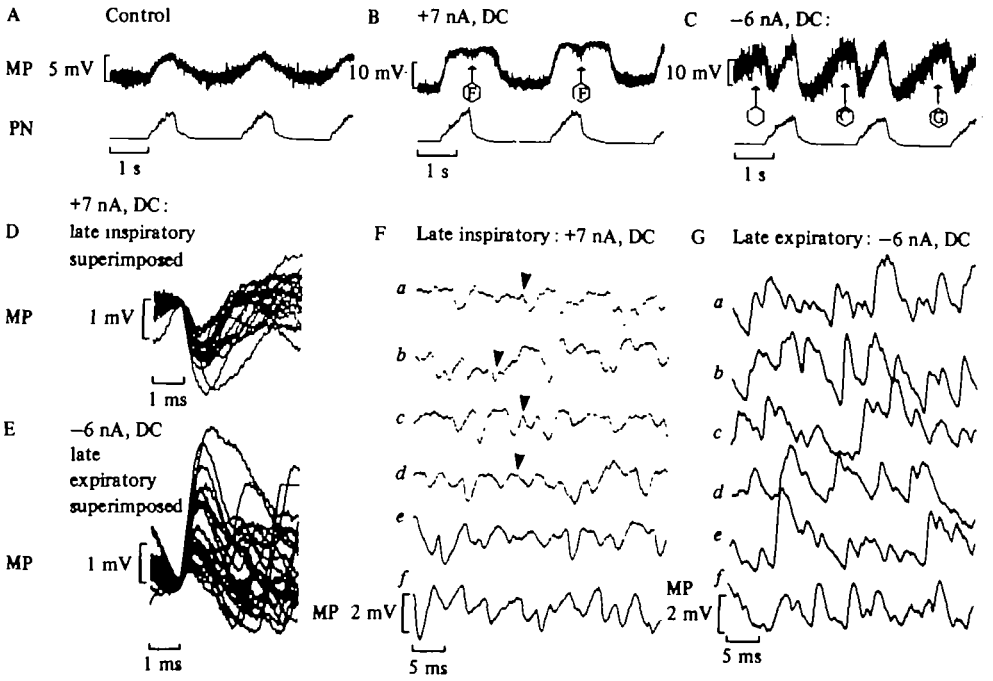

Fig. 3. Changes in the membrane potential (MP) of an alpha type inspiratory interneurone showing i.p.s.p. reversal following positive (B, D, F) and negative current injection (C, E, G). PN: integrated phrenic nerve activity. In traces F and G the postsynaptic potentials are shown in several fast sweep recordings (*a–f*) at the times indicated by the insets F and G in traces B and C. Hyperpolarizing late inspiratory i.p.s.p.s are superimposed in D and reversed i.p.s.p.s during stage 2 expiration are superimposed in E. The recordings were from a pentobarbital anaesthetized cat.

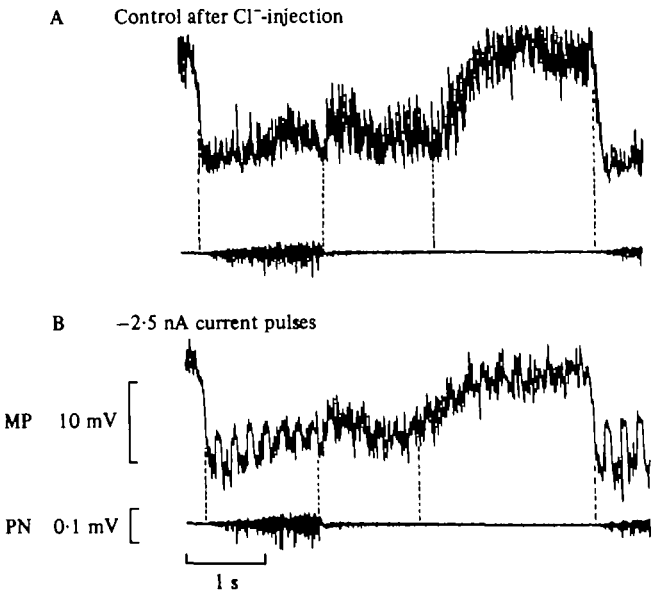

Fig. 4. Membrane potential (MP) recorded in a beta type inspiratory interneurone after injection of chloride ions has reversed i.p.s.p.s in A; the voltage responses to injected −2·5 nA current pulses of 100 ms duration showing reduction in input resistance during late inspiration, during stage 1 expiration and during stage 2 expiration in B. The bridge is overcompensated by 10^6 ohms. PN: phrenic nerve activity. The recordings were made from a pentobarbital anaesthetized cat.

expiration starts (Fig. 3, 4, 6). Neurone input resistance falls significantly (Fig. 4B) and the membrane is strongly polarized. As this period is often sufficiently long, the equilibrium potential of the chloride sensitive i.p.s.p.s is sometimes attained. Negative current and chloride ion injections reverse the polarity of these i.p.s.p.s indicating that the relevant synapses are located near to the soma. An augmenting pattern of reversed i.p.s.p.s becomes evident (Fig. 3C, 4) which closely resembles the discharge pattern of expiratory neurones within the rostral and caudal brainstem.

The patterns of postsynaptic activity in these inspiratory neurones indicate once again that the respiratory cycle consists of 3 phases: i.e. firstly an inspiratory ramp-like excitatory activity which is finally shunted by a short-lasting inhibition; secondly a period when excitatory and inhibitory inputs are interacting to various degrees in different types of neurone; and thirdly a ramp-like inhibition during stage 2 of expiration. These findings disagree with the two stage model of central rhythmogenesis of Salmoiraghi & Baumgarten (1961) in which a two phase oscillation of respiration is produced by reciprocal interactions between inspiratory and expiratory neurones. The findings are much more consistent with the theory of Bradley *et al.* (1975) that there exists an inspiratory 'ramp generator' controlled by its own 'off-switch' and that the expiratory activity is only part of an inhibitory system keeping the inspiratory neurones depressed (Euler, 1977; Euler & Trippenbach, 1976; Euler *et al.* 1973).

HIGHER ORDER INTERNEURONES AND THEIR ROLE IN RHYTHMOGENESIS

How can the concept of a 'ramp generator' (Bradley *et al.* 1975) and reversible and irreversible 'off-switch' (Younes, Remmers & Baker, 1978) be explained by neurophysiological mechanisms?

The composition of the ramp generating system is still unknown, but some features can be predicted. As there is obviously no cellular respiratory pacemaker this ramp generation may be supposed to result from chemical or electrical synaptic interactions between inspiratory neurones, their activity being started by activation from the reticular formation (Hugelin & Cohen, 1963; Salmoiraghi & Burns, 1960*b*). Once activated, inspiratory neurones may summate this activity in a recurrent excitatory loop network formed by their axon collaterals. Positive cross-correlations between inspiratory neurones support this possibility. (Cohen, 1976; Feldman *et al.* 1980; K. P. Madden, J. P. Baker & J. E. Remmers, in preparation). However, not all types of inspiratory neurone can be included in such a system. Besides a transient 'off-switch' at the end of inspiration the system needs to be 'gated' during stage 1 of expiration until expiratory neurones are activated and keep the inspiratory system depressed by antagonistic inhibition. Bulbospinal and higher order alpha and beta inspiratory neurones which continue to discharge during the postinspiratory phase obviously are excluded from the ramp generator: their declining pattern of firing during stage 1 of expiration would tend to produce a new inspiratory ramp activity before expiration could start and allow air to flow out of the lungs. The basic properties of the ramp generator neurones is assumed to be an accumulating ramp-like excitation during the inspiratory phase and a powerful inhibition not only during the end of the inspiratory phase but also during both stages of expiration.

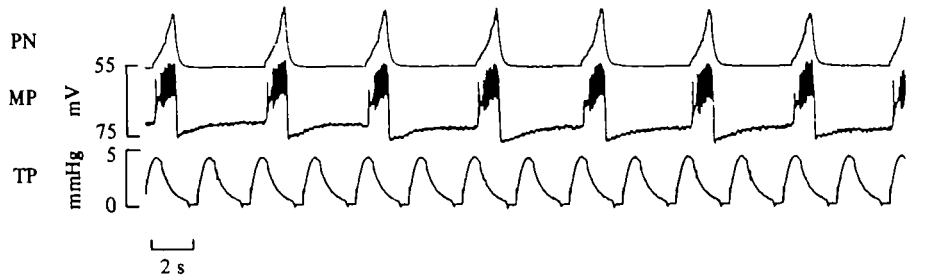

Fig. 5. Postinspiratory 'gating'. Membrane potential (MP) of an alpha type inspiratory 'ramp' interneurone showing an augmenting discharge during inspiration and inhibition during both stages of expiration. PN: integrated phrenic nerve activity. TP: tracheal pressure of the pentobarbital anaesthetized, thoracotomized and artificially ventilated cat.

This behaviour is found in some higher order interneurones (Fig. 5). They are active in a ramp-like fashion during inspiration and are powerfully inhibited at the end of inspiration and during both stages of expiration. When inhibition is removed towards the end of stage 2 of expiration these neurones are steeply depolarized and some of them discharge 2–3 action potentials at short intervals and at fairly low firing levels which may be the result of rebound excitation. These neurones then continue to depolarize steadily, discharging an augmenting burst of action potentials throughout inspiration. After inspiration the membrane is steeply hyperpolarized by i.p.s.p.s, with maximal levels of membrane potentials being reached at the beginning of stage 1 of expiration when neurone input resistance is effectively reduced. Membrane hyperpolarization gradually declines in parallel with postinspiratory activity in the phrenic nerve but these neurones remain inhibited during state 2 of expiration. It is a consistent finding that this late expiratory inhibition has a plateau pattern which is quite different from the discharge pattern of most medullary expiratory neurones but very similar to that of expiratory laryngeal motoneurones (Barillot & Bianchi, 1971; Barillot & Dussardier, 1976; Cohen, 1977). This suggests that the laryngeal neuronal network may be much more important in the rhythmogenesis of respiration than was previously thought.

The discharge of the inspiratory ramp generator is assumed to represent the central inspiratory drive (CID) to the other inspiratory 'follower' cells (Wyman, 1977; Bradley *et al.* 1975). How is this CID 'off-switched'? The inspiratory inhibitory inflation reflex (Hering, 1868; Breuer, 1868) serves only as a trigger to terminate inspiration (Wyman, 1977). Therefore, there must be a central 'off-switch' mechanism. The threshold to activate this mechanism steadily decreases with inspiration and it is generally believed that it is controlled by the inspiratory activity itself (Baker & Remmers, 1980; Bradley *et al.* 1975; Cohen & Feldman, 1977). This implies the existence of an inspiratory inhibitory system which is maximally active at the end of inspiration.

Late inspiratory neurones may be the proper candidates and some of these late inspiratory neurones may even be beta type cells receiving additional inputs from lung stretch receptors. The long delay in the activation of these late inspiratory neurones has been explained by a weak convergence of excitatory inputs from the CID and a

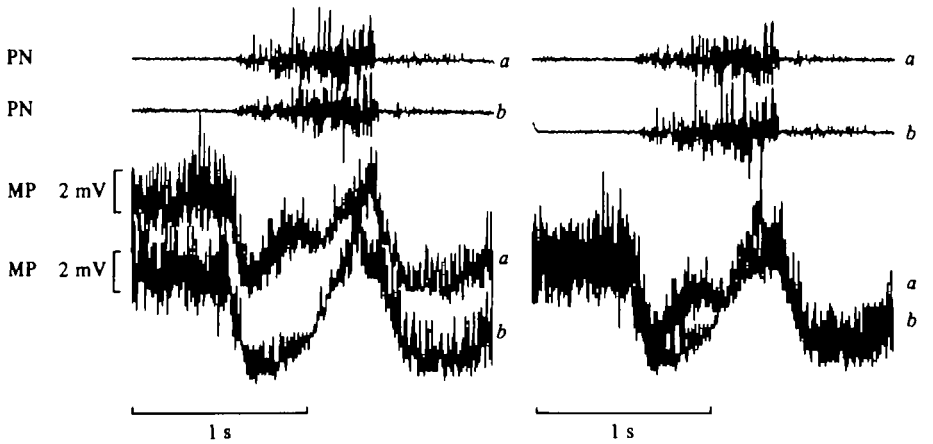

Fig. 6. A late discharging inspiratory neurone revealing inhibition during early inspiration and stage 2 expiration. After chloride ion injection stage 2 expiratory i.p.s.p.s reversed before (trace b) early inspiratory i.p.s.p.s (trace a). The DC level of the membrane potential of trace a and b was identical. The traces are separated on the left side and superimposed on the right side of the figure for better comparison. MP: membrane potential. PN: phrenic nerve activity. The recordings were made from a pentobarbital anaesthetized cat.

high threshold for excitation (Cohen & Feldman, 1977) but no evidence for these features has been found in intracellular recordings. Rather, these higher order interneurones are powerfully inhibited during the first half of inspiration, receiving a pattern of i.p.s.p.s which shunts all incoming excitatory inputs (Fig. 6). Actually e.p.s.p.s with an augmenting pattern arrive from the very beginning of inspiration and may represent the CID. As early inspiratory inhibition is progressively removed excitation starts to become effective and the neurones are depolarized, discharging a burst of action potentials at the end of inspiration. This discharge behaviour closely resembles the late inspiratory i.p.s.p pattern seen in alpha bulbospinal and inspiratory interneurones. These late inspiratory interneurones may, therefore, represent the central inspiratory 'off-switch' mechanism.

Late inspiratory neurones do not discharge during stage 1 of expiration and they recieve an augmenting pattern of i.p.s.p.s during stage 2 of expiration. Their presumed inspiratory 'off-switch' function acts, therefore, only during late inspiration. Inhibition of the ramp generator during stage 1 of expiration would have to be explained by different mechanisms.

The early inspiratory inhibition of late inspiratory neurones is of a declining character and resembles the discharge behaviour of early inspiratory higher order interneurones, which are known to have a very rich arborization of their axon terminals within the medulla and are assumed to accommodate quickly in their discharge (Merrill, 1974). These cells are steeply depolarized when inspiration starts and discharge a short burst of action potentials with a declining pattern (Fig. 7). There is no evidence as yet for rebound excitation and, as the membrane slowly repolarizes during inspiration, they may cease firing as a result of inhibitory synaptic inputs. During the postinspiratory period these neurones are strongly inhibited by a declining pattern of i.p.s.p.s; this inhibition is less prominent during stage 2 of expiration.

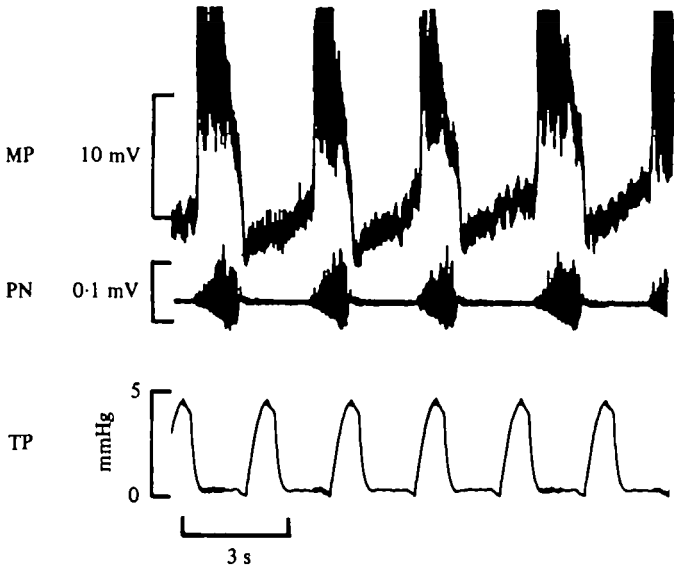

Fig. 7. Membrane potential pattern (MP) of an early inspiratory interneurone. PN: phrenic nerve activity. TP: tracheal pressure of the pentobarbital anaesthetized, thoracotomized and artificially ventilated cat.

The primary function of postinspiratory activity seems to be one of depressing both inspiratory higher order and expiratory activities. In the ventilatory cycle expiration starts 'passively' when inspiratory muscles slowly relax and in order to smooth ventilatory movements, activation of the expiratory muscles should be delayed. At the same time expiratory airflow is actively controlled by laryngeal adductor muscles. In neurophysiological terms recycling excitation within the inspiratory ramp generating system needs to be 'gated' over a considerable time so as to avoid inspiratory apneusis or rapid shallow breathing and, in order to slow the frequency of respiration, this 'gate' has to delay the onset of expiratory activity. The primary function of postinspiratory activity seems, therefore, to be one of depressing both inspiratory higher order and expiratory activities.

In inspiratory neurones the action of the 'gate' is seen in the powerful inhibition of the early inspiratory and 'inspiratory ramp' interneurones. Its action on 'caudal' expiratory neurones is disinhibitory and disfacilitatory. The analysis of i.p.s.p. patterns arriving at these expiratory neurones reveals inhibition during the inspiratory ramp phase (Fig. 8) but during stage 1 of expiration they are disinhibited and their input resistance increases. Disinhibition, however, does not seem to be the only effect. Whenever postinspiratory activity is prolonged and disinhibition comes to an end activation of expiratory neurones is delayed (Fig. 9). Therefore, disinhibition is followed by disfacilitation. This effect is consistent with the idea that active expiratory movements should be delayed in order to allow stage 1 of expiration to occur. Comparable information about the synaptic behaviour of expiratory neurones located in the rostral areas of the medulla (Lipski & Merrill, 1980; Merrill, 1970, 1981) is not yet available.

The depressive action of postinspiratory activity is seen also in 'nonrespiratory'

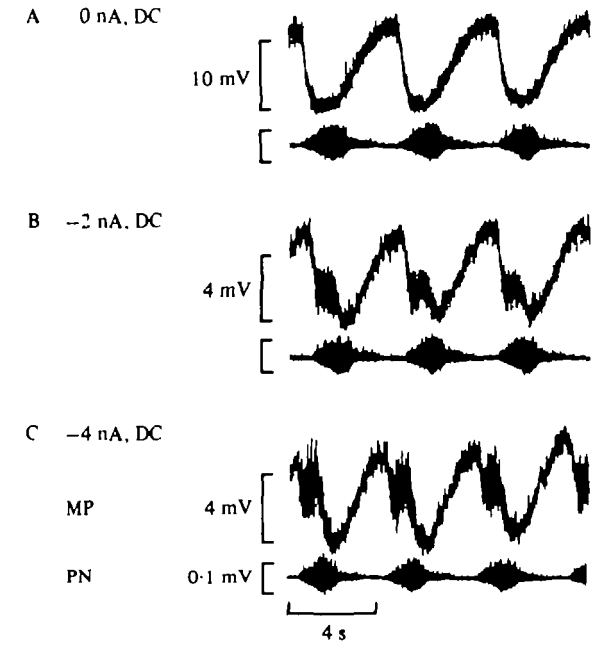

Fig. 8. Membrane potential pattern (MP) of an expiratory bulbospinal neurone before (A) and during negative DC current injection (B and C). PN: phrenic nerve activity. The recordings were made from a pentobarbital anaesthetized cat.

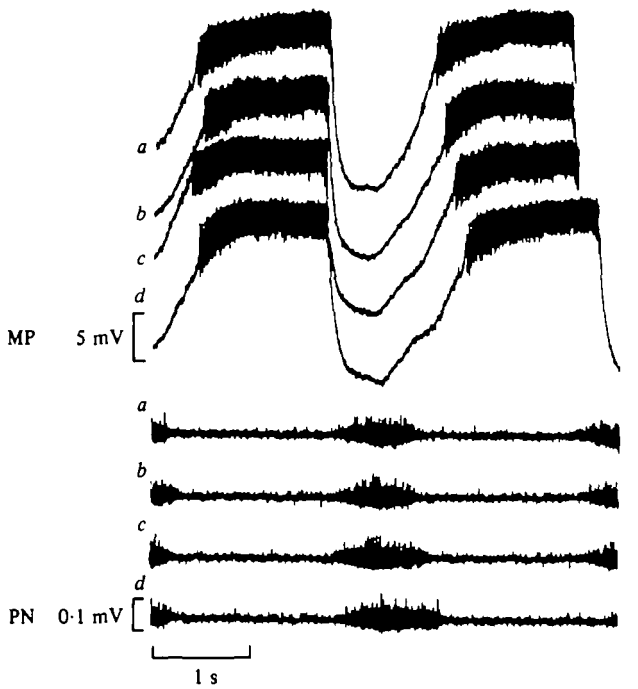

Fig. 9. Membrane potential patterns (MP, *a–d*) of an expiratory bulbospinal neurone during different patterns of phrenic nerve discharge (PN). The duration of postinspiratory discharge in the phrenic nerve is progressively increased from *a* to *d*. The recordings were made from a pentobarbital anaesthetized cat.

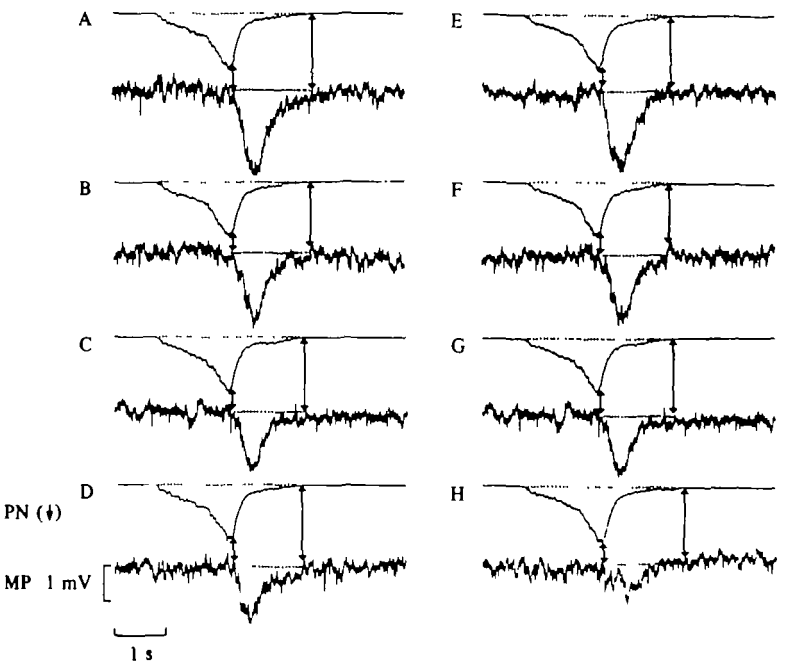

Fig. 10. Membrane potential patterns (MP) recorded in a neurone of the medullary reticular formation showing rhythmic hyperpolarization locked to the postinspiratory discharge in the phrenic nerve (PN). The phrenic nerve activity is shown in its integrated form with increasing frequency indicated by a downward deflection. The arrows indicate the postinspiratory period. The recordings were made from a pentobarbital anaesthetized cat.

neurones, i.e. neurones discharging tonically almost throughout the respiratory cycle and whose membrane potential shows no inspiratory or expiratory ramp depolarization (Fig. 10). The only feature which relates these neurones to respiration is a prominent wave of i.p.s.p.s and a concomitant decrease in their input resistance during postinspiratory activity in the phrenic nerve. Asumming that neurones of this type are involved in the reticular activating system (Hugelin & Cohen, 1963) this finding would indicate an even more widely distributed depressant action of postinspiratory activity (D. W. Richter & D. Ballantyne, in preparation).

Postinspiratory neurones are themselves antagonistically depressed by inspiratory and expiratory neurones (Fig. 11). They are synaptically inhibited during stage 2 of expiration and particularly strongly inhibited during inspiration. The latter inhibition is most intense during early inspiration while i.p.s.p.s arriving during stage 2 of expiration show an augmenting pattern. This suggests that postinspiratory neurones would be tonically active were rhythmic inspiratory and expiratory activities to fail. The common inhibitory function of postinspiratory neurones, therefore, seems to be effectively controlled by the medullary inspiratory and expiratory neurones. It achieves a temporal separation of inspiration from stage 2 of expiration and smooths respiratory movements.

The results described in this article could be explained by the following type of model:

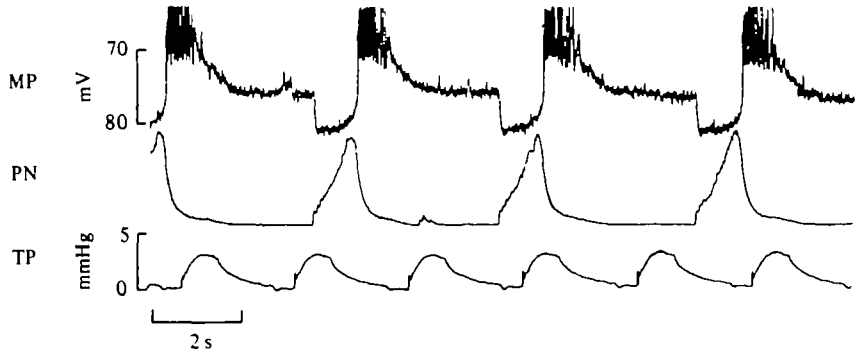

Fig. 11. Membrane potential pattern (MP) of a postinspiratory interneurone and integrated phrenic nerve activity (PN) in a pentobarbital anaesthetized, thoracotomized and artificially ventilated cat. TP: tracheal pressure.

There are higher order interneurones showing a ramp-like activation after being released from inhibition. This central inspiratory activity is 'off-switched' by late inspiratory interneurones which receive both a central inspiratory drive (CID) and an inhibitory input from early inspiratory neurones. The activity of the latter declines, probably because they are inhibited during late inspiration. Subsequently the 'ramp generator' is immediately 'gated' by a powerful inhibition. This postinspiratory inhibition, therefore, seems to be one of the most important mechanisms in the rhythmogenesis of central respiration. Functionally, it allows stage 1 of expiration to occur. Inhibition at the end of stage 1 of expiration is much weaker and if excitatory inputs predominate a new inspiratory ramp may be started before expiratory neurones are released from disfacilitation. This would result in rapid shallow breathing which is known to occur under various circumstances. If expiratory neurones become activated then the ramp generator is again inhibited and the frequency of ventilation is markedly slowed.

The experiments from which Fig. 1 is taken were performed in collaboration with Drs C. Bainton, D. Ballantyne, J. Klein and J. Remmers. I am grateful to each of them and also to Prof. H. Seller for helpful discussions. This work was supported by the DFG.

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