

MECHANISMS OF CENTRAL TRANSMISSION OF RESPIRATORY REFLEXES

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Abstract. Several types of respiratory reflex actions can be discerned according to the reactions of typical respiratory neurons in the efferent part of the central rhythmogenic structure. Whereas respiration runs closely parallel with inspiratory neuron activity the behaviour of expiratory neurons cannot be derived from the resulting reflex changes of respiration. So expiratory apnoea can be combined with continuous activity or with inactivation of expiratory neurons. Extracellular records from a closed uniformly reacting population of expiratory neurons and from neighbouring reticular neurons allowed experimental differentiation between different types of central respiratory reflex actions. In experiments on anaesthetized dogs the responses to chemoreceptor and baroreceptor excitation and to pulmonary inflation were investigated. Chemoreceptor excitation leads to activation of inspiratory, expiratory, and reticular neurons, whereas the baroreceptor afferents act in the opposite direction. In contrast moderate lung inflation causes more specific effects: activation of expiratory neurons, inactivation of inspiratory neurons. But if a certain degree of lung inflations is exceeded a more general inhibition of both inspiratory and expiratory neurons takes place. These results only apply to the "typical" respiratory neurons. The principles used to distinguish between the different types of reflexes are proposed for a basis of classification also of other neural, chemical or pharmacological influences on breathing.

The mode of central respiratory reflex transmission is still fairly unknown. The peculiarity in comparison with other reflex centres is that at least partly the same complicated network of brain stem neurons is involved which also generates the respiratory rhythm. As long as the fundamental process of central rhythmogenesis is not fully understood, also respiratory reflex transmission will be a partly unsolved problem. In spite of this some general principles can be derived from the reactions of certain groups of respiratory neurons.

Figure 1A shows a simple functional scheme of this structure in order to demonstrate the different possibilities of respiratory reflex transmission. This scheme is based on the following fairly well established facts. There are two populations of respiratory neurons, one inspiratory the other expiratory, which are alternately active and have mutual reciprocal inhibitory connexions. The inspiratory neurons partly activate

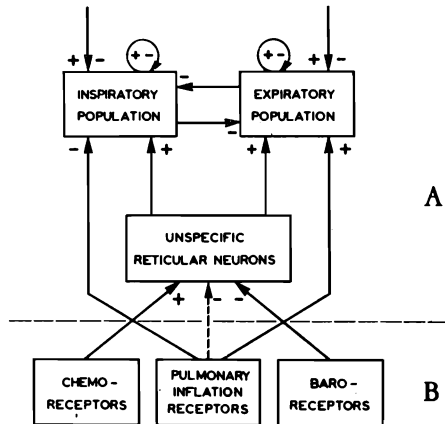


Fig. 1. Schematic drawing of the basic functional structure in typical brain stem respiratory and unspecific reticular neurons (A) and the probable mode of action of various types of respiratory reflex afferents on this system (B). The arrows from above represent the influences from higher structures of the neuraxis, and the circles represent the facilitatory and inhibitory feedback mechanisms within the respiratory populations. Interrupted line: effect of strong and/or rapid lung inflation. It should be noted that besides the drawn indirect actions via unspecific general activation or inactivation, direct connexions from chemoreceptor and baro-receptor afferents to inspiratory and expiratory neurons are not excluded by the experiments. The given scheme is the simplest possible interpretation of the present findings.

inspiratory motoneurons thus causing inspiration, the expiratory neurons discharge during the non-inspiratory phase and at least some of them can activate expiratory motoneurons. The activity in this structure is closely related to general reticular activity (Salmoiraghi and Burns 1960) and activation of respiratory neurons can be one part of a general reticular activation (Hugelin and Cohen 1963).

The following three types of respiratory reflexes will be considered: (i) those increasing respiration, (ii) those depressing respiration, and (iii) those shifting the relation between inspiratory and expiratory activity. Because these reflexes act on the central rhythmogenic apparatus sketched before several types of reflex mechanisms are possible (Table I).

TABLE I

Compilation of the different possible reactions of typical inspiratory, expiratory, and reticular neurons underlying driving and depressing respiratory reflexes

Type	Reflexes driving respiration			Reflexes depressing respiration		
	Typical inspiratory neuron	Typical expiratory neuron	"Unspecific" reticular neuron	Typical inspiratory neuron	Typical expiratory neuron	"Unspecific" reticular neuron
<i>a</i>	↑	↓	—	↓	↑	—
<i>b</i>	↑	↓	—	↓	↑	—
<i>c</i>	↑	↑	↑	↓	↓	↓
<i>d</i>	↑	↑	—	↓	↓	—

Reflexes driving respiration can operate by:

a) Primary activation of inspiratory neurons combined with reciprocal secondary inhibition of expiratory neurons.

b) Primary inhibition of expiratory neurons which in time will lead to disinhibition of inspiratory neurons.

c) General activation of reticular activity causing increased firing of inspiratory as well as expiratory neurons.

d) Specific activation of inspiratory as well as expiratory neurons without involvement of "unspecific" reticular neurons.

By means of extracellular recordings from respiratory and reticular neurons only the type *a* and *b* respiratory drive can be distinguished from *c* and from *d*, but not *a* from *b*. For reflexes depressing respiration the same considerations are applicable but with the inverse sign (right part of Table I). Table I also makes clear that records from inspiratory neurons cannot help to differentiate between the different types of reflex activation or depression of respiration. Therefore we have concentrated our studies mainly on expiratory neurons.

Another consequence of the functional structure shown in the upper part of Fig. 1 is that two kinds of respiratory arrest in expiratory position are possible which cannot be differentiated by recording inspiratory impulses or respiratory movements: (i) The general activity in the system can be diminished to such a degree that respiratory neurons cease to fire all together. We have called this state "inactive apnoea". (ii) Expiratory neurons can be continuously active while only inspiratory activity ceased, which is called „arrhythmic apnoea" (Koepchen et al 1970) (Fig. 2). Arrhythmic apnoea gives an opportunity to study direct actions on expiratory neurons apart from responses caused indirectly by way of action on the inspiratory population (see below).

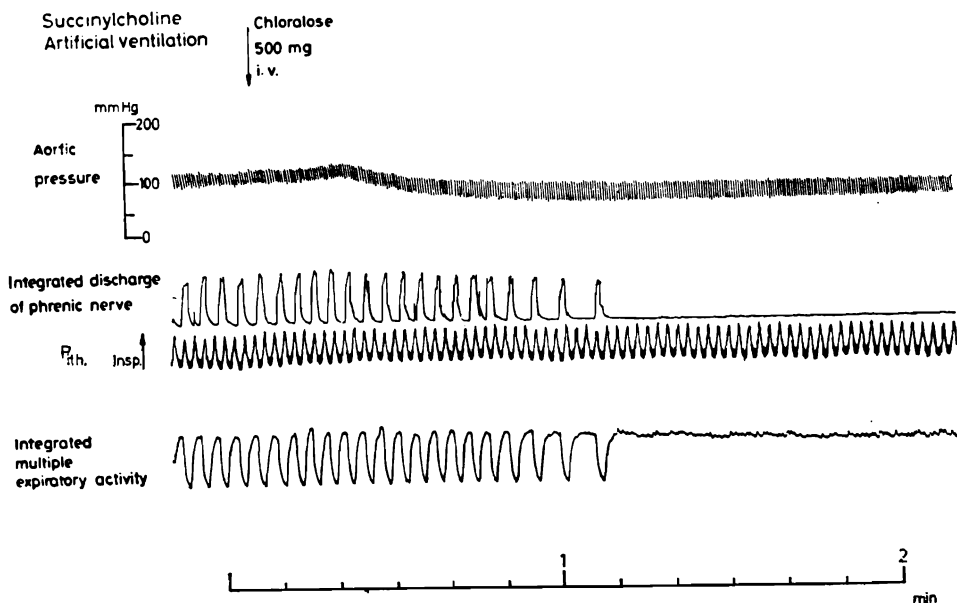


Fig. 2. Time course of multiple neuronal activity in the centre of the typical expiratory population during generation of arrhythmic apnoea induced by an overdose of chloralose. P_{ith} : intrathoracic pressure recorded by means of a balloon in the oesophagus. Inspiration goes upwards during artificial ventilation after immobilization with succinylcholine.

The scheme of Table I may be valid only for the efferent part of the system whereas in the proper central interneurons other kinds of reaction are conceivable. For the efferent part of the *inspiratory* neurons phrenic nerve activity is a good indicator. A closed population of *expiratory* neurons was localized by Philipp and Klüssendorf (1969) in the dog caudo-lateral to the obex. This localization roughly agrees with statements of other authors for the cat (Baumgarten et al. 1957, Haber et al. 1957, Nelson 1959, Batsel 1964, Merrill 1970, Bianchi 1971) but in the dog this expiratory area is still more extensive and sharply limited against the surrounding non-respiratory reticular regions. Within this area all neurons react in the same manner in the course of respiratory reflexes as in the example of Fig. 3. Here during the inhibition caused by blood pressure increase the activity of one single expiratory neuron is separated by electronic means from the background activity recorded with the same electrode. As can be seen the single neuron activity runs closely parallel with that in the surrounding expiratory population.

Stimulation through the recording electrode in the centre of this region leads to expiratory arrest of respiration (Fig. 4). Stronger stimuli cause forced expiratory movements. On the other hand the burst activity

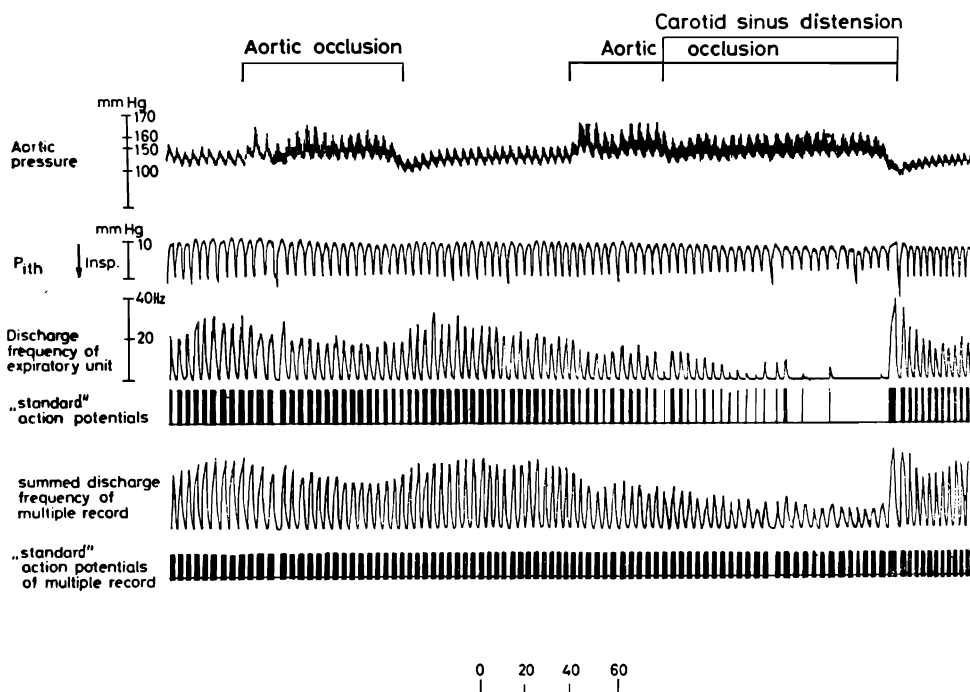


Fig. 3. Neuronal activity in the centre of the typical expiratory population from several neighbouring neurons (lower record) recorded with the same microelectrode during reflex changes caused by baroreceptor excitation. At the same time activity of one single neuron is separated from the background of multiple activity by electronic means (upper record). The reflex changes of discharge frequency run closely parallel in the multiple and single unit records demonstrating the uniformity of reaction in the whole recorded population.

within this area is diminished after stimulation in the inspiratory region adjacent rostrally. Therefore it seems to be justified to call these neurons: "typical expiratory neurons". Their function is (i) to cause expiration, and (ii) to inhibit inspiratory activity. The following analysis of reflex effects is based on this special group of expiratory neurons in dogs anaesthetized with chloralose-urethane.

As a prototype for *activating reflexes* the *chemoreceptor reflexes* were investigated, because there are contradictory findings concerning the chemoreflex action on expiratory neurons (Baumgarten 1956, Batsel 1965, Nesland et al. 1966). We found that chemoreceptor stimulation caused by i.v. injection of lobeline (0.05 mg/kg) activated both inspiratory and expiratory neurons (Fig. 5). The impulse pattern was analysed by computer: during chemoreceptor stimulation the mean frequency of impulses during the bursts and the number of impulses/time were increased

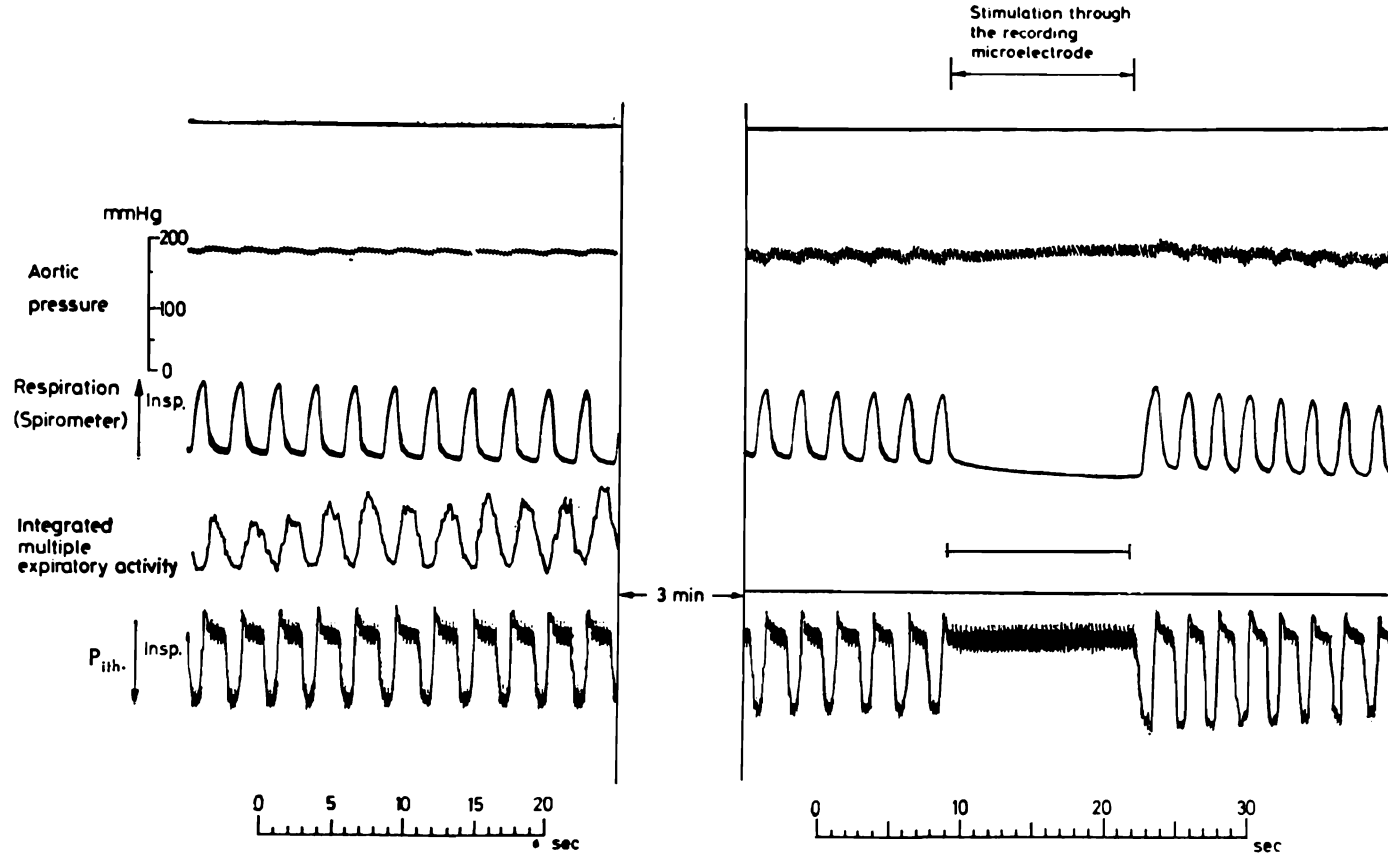


Fig. 4. Record from the centre of the typical expiratory population (left), and effect of stimulation at the same site through the microelectrode used before as recording electrode (right). Respiration registered by the aid of a spirometer and simultaneously by a balloon in the oesophagus. Total arrest of respiration in expiratory position during the stimulation period.

in both populations whereas the duration of bursts diminished in expiratory neurons.

It might have been possible that the activation of expiratory neurons during chemoreceptor stimulation was the expression of some kind of "rebound" after release from a stronger inhibition in the inspiratory phase caused by the augmentation of inspiratory bursts. To test this hypothesis we applied the chemoreceptor stimulus during the state of

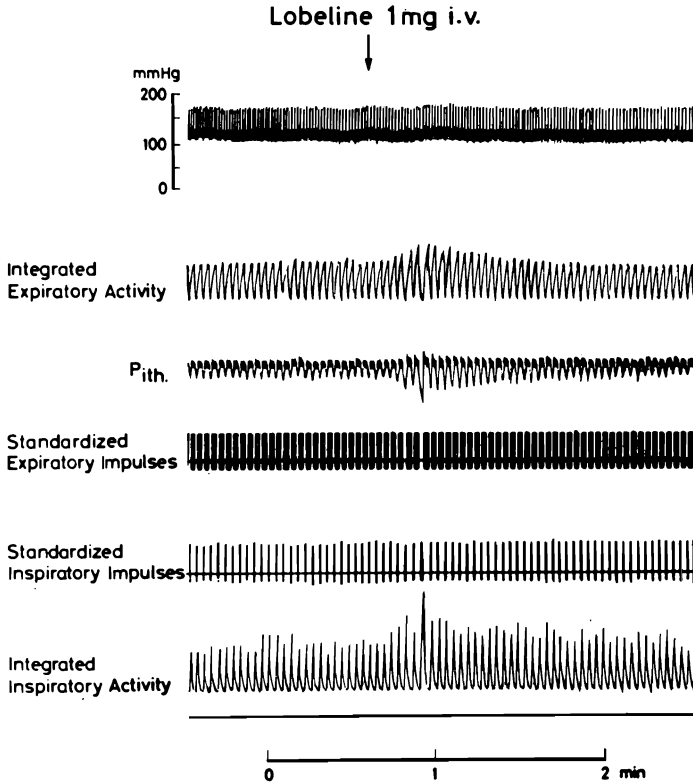


Fig. 5. Simultaneous multiple records with two microelectrodes, one from the expiratory region the other one from the ventral inspiratory region at the level of the obex. Both populations are activated after i.v. injection of a low dose of lobeline, which was ineffective after denervation of the peripheral chemoreceptors.

expiratory arrhythmic apnoea produced by a higher dose of chloralose (Fig. 6). In this instance also expiratory neurons were activated by chemoreceptor excitation in the absence of inspiratory activity. That means that chemoreceptor afferents excite expiratory neurons independently of their action on inspiratory neurons. In other experiments the response of surrounding non-respiratory reticular neurons to chemore-

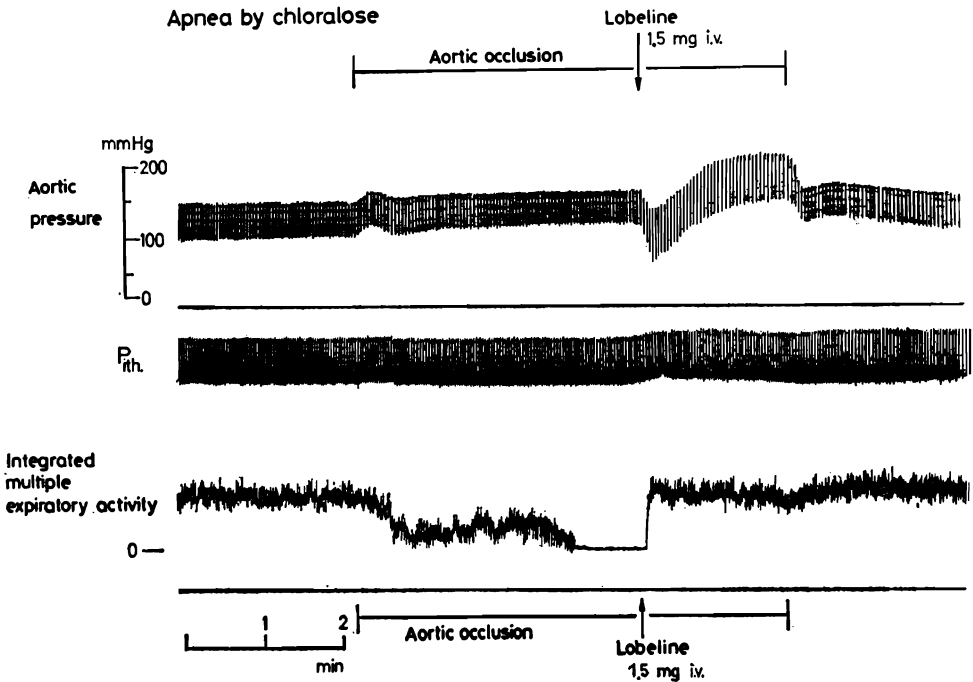


Fig. 6. Reflex effects on the integrated typical multiple expiratory activity during arrhythmic apnoea induced by chloralose. Artificial ventilation by a Starling pump. Blood pressure increase during aortic occlusion depresses neuronal activity until complete arrest whereas chemoreceptor stimulation by lobeline restores the expiratory activity in spite of the elevated blood pressure.

ceptor stimulation was recorded. For most of the tested reticular neurons chemoreceptor excitation likewise led to increased activity (P. Langhorst and H. P. Koepchen, unpublished data). Therefore the chemoreceptor reflex increase of breathing is a generally activating reflex according to case c in Table I.

The known inhibition of respiration by arterial *baroreceptor* afferents (Heymans and Bouckaert 1930) was investigated as an example of an *inhibitory respiratory reflex*. As was expected inspiratory neurons were inhibited during the reflex hypopnoea of baroreceptor origin. The effect on the typical expiratory neurons is more complicated: the decrease of respiratory frequency is accompanied by prolonged expiratory bursts. Accordingly the number of impulses per burst is augmented, but on the other hand the discharge frequency during these prolonged expiratory bursts is diminished. Similar findings have been described in the cat (Gabriel and Seller 1969), but the question remained unsettled if these changes in the discharge pattern of expiratory neurons under the influ-

ence of the baroreceptor input may be interpreted as activation or inhibition. More conclusive results can be obtained if the decrease of respiratory frequency during the blood pressure increase is prevented by artificial ventilation. In this case all parameters of expiratory burst activity decrease (Klüssendorf et al. 1970). This inhibition also can be obtained if the blood pressure during baroreceptor excitation is held constant (Fig. 7). As in the case of chemoreceptor stimulation the baroreceptor reflex

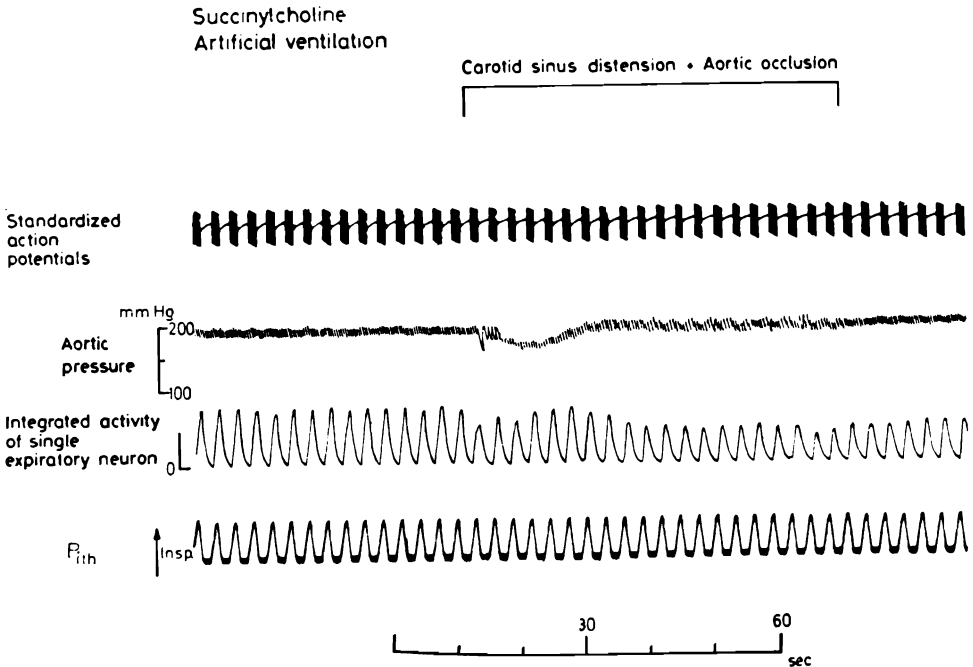


Fig. 7. Effect of baroreceptor stimulation on single neuron activity in the typical expiratory region during constant respiratory frequency triggered by artificial ventilation in the immobilized dog. Both carotid sinuses were distended by intraluminal balloons and aortic pressure was adjusted by gradual inflation of an intra-aortic balloon. Note the immediate drop of discharge frequency after the beginning of carotid sinus distension. The following reflex decrease of blood pressure is accompanied by reactivation of the expiratory neuron. At this moment arterial pressure was brought to the control level by partial aortic occlusion. The restoration of blood pressure depresses again the expiratory activity, which remains lowered as long as carotid sinus distension is maintained.

effect on expiratory neurons is still present during arrhythmic expiratory apnoea (see Fig. 6), and therefore cannot be a secondary consequence of primary action on the inspiratory population.

In earlier work we found that 75% of the reticular neurons in the same region of the brain stem reacting to blood pressure changes are

inhibited (Koepchen et al. 1967). Thus the baroreceptor reflex can be classified as a generally inhibiting reflex and is the mirror-image of chemoreflex excitation (see column c in Table I).

The most important examples of *reflexes changing the balance between inspiratory and expiratory activity* are the mechano-reflexes from the lungs (*Hering-Breuer reflexes*). Some details of the central reflex action of pulmonary inflation and deflation have been described elsewhere (Klüssendorf and Koepchen 1969, Koepchen et al. 1971). In a limited range of lung volume changes we could confirm in the dog the excitation of expiratory neurons and the inhibition of inspiratory neurons described in experiments on cats and rabbits (Hukuhara et al. 1956, Baumgarten and Kanzow 1958, Koepchen and Baumgarten 1958, Nesland and Plum 1965, Cohen 1969).

But we found some remarkable peculiarities in the response of expiratory neurons to lung distension which will be discussed here in so far as they are related to the classification of pulmonary distension reflexes in the scheme mentioned above.

Records from the centre of the typical expiratory neuron population

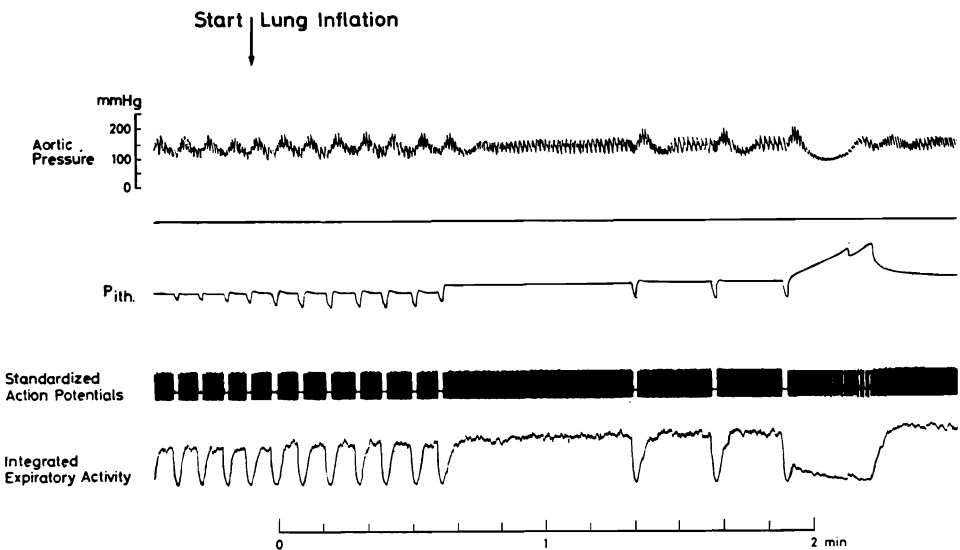


Fig. 8. Effect of lung inflation on multiple activity in the expiratory population. Stepwise increase of pulmonary distension produced by continuous blowing of O_2 into the open tracheal tube causes a stepwise increase of the level of expiratory activity together with the prolongation of the bursts. Further increase of intra-pulmonary pressure (at the right) depresses the activity of the same neurons. If the overdistension is somewhat reduced, increased expiratory discharge frequency reappears.

showed that during gradual inflation of the lungs the same neurons whose discharge frequency increased during moderate inflation were inhibited at higher degrees of inflation (Fig. 8). This inhibition of expiratory neurons was observed even at moderate lung volumes if the rate of inflation was increased. The secondary inhibition of expiratory neurons at higher lung volumes is not accompanied by inspiratory efforts or phrenic nerve activity and therefore cannot be related to the Head's (1889) "Paradoxical reflex". That means that under certain conditions expiratory, as well as inspiratory activity is depressed by pulmonary inflation. At these higher ranges of lung inflation we could observe also inhibition of unspecific reticular activity (Koepchen 1969, Fig. 8).

These findings suggest that two components of the lung inflation reflex may be discerned: the first one shifting the balance between central inspiratory and expiratory activity in favour of the latter, and the other one causing general central depression analogous to the baroreceptor reflex (see Table II). We have no information yet as to whether these two components are due to the action of different groups of pulmonary receptors or to the different response of expiratory neurons dependent on the frequency in the afferent vagal fibres.

In arrhythmic states (chloralose apnoea and hyperventilation apnoea) we never could observe the activation of the typical expiratory neuron population during moderate lung inflation, which was present in the same neurons in the case of intact central respiratory rhythm. Only inhibition was achieved by all degrees and rates of lung inflation during the arrhythmic states.

TABLE II

Schematic representation of the results obtained in the reflex studies on respiratory and reticular neurons. The responses to baroreceptor stimulation, chemoreceptor stimulation, and strong and/or rapid lung inflation correspond to the type *c* reaction in Table I, i.e. general activation or inactivation of reticular activity

Respiratory stimuli	Inspiratory neuron		Expiratory neuron		Reticular neuron
	Rhythmic state	Arrhythmic state	Rhythmic state	Arrhythmic state	
Chemoreceptor stimulation	↑		↑	↑	↑
Baroreceptor stimulation	↓		↓	↓	↓
Moderate and slow Pulmonary inflation	↓		↑	↓	—
Strong and/or rapid	↓ (↑)		↓	↓	↓

The scheme in Table II and Fig. 1 comprise the findings and give the basis for the suggested classification of the studied respiratory reflexes. It should be noted that our present data on expiratory neurons are much more complete than those on inspiratory neurons. Of course such a simple classification in the first instance pertains only to "typical" respiratory neurons representing the efferent part of the rhythmogenic system. The closed expiratory population described above probably belongs to this efferent part, just as those inspiratory neurons reacting in the same manner are related to phrenic nerve activity.

Bearing in mind this limitation it would be useful to consider also other nervous, chemical and pharmacological influences on the respiratory centres with regard to their position in the outlined scheme.

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