# VAGAL INFLUENCES ON RESPIRATORY REFLEXES: INTERACTION OF P.S.R. AND R.A.R. ON THE INFLATION AND DEFLATION REFLEX, THEIR ROLE IN LINKING RESPIRATORY CYCLES; AND POSTVAGOTOMY EFFECT OF P.D.G.

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ABSTRACT

VAGAL INFLUENCES ON RESPIRATORY REFLEXES: INTERACTION OF P.S.R. AND R.A.R. ON THE INFLATION AND DEFLATION REFLEX, THEIR ROLE IN LINKING RESPIRATORY CYCLES; AND POSTVAGOTOMY EFFECT OF P.D.G.

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There is evidence that changes in one respiratory cycle may influence subsequent cycles by a central mechanism. Thus the influence of P.S.R. and R.A.R. activity from within one respiratory cycle on subsequent cycles, which we have called "memory", needed to be examined in the determination of duration of expiration (tE) and inspiration (tI).

This study was designed to investigate the relative roles of P.S.R. and R.A.R. stimulation in expiration influencing tI amd tE over several subsequent breaths. In particular to investigate their role in linking respiratory cycles.

In 14 anaesthetized spontaneously breathing rabbits we studied the response of tI and tE to +ve and -ve pressure pulses of 20KPa applied to the lung at various stages in expiration before and during P.S.R. block with SO2.

Before P.S.R. block, +ve pressure pulses early in expiration generally shortened tE containing the pulse, applied later +ve pressure pulses lengthened tE. Positive pressure pulses after P.S.R. block,

and -ve pressure pulses before and after block always shortened tE. Regardless of sign of pulse tE was shortened in subsequent breaths before and after block.

The inspiration after negative pulse application was usually lengthened. After effective block -ve pulses rarely lengthened tI. Large shortening of tE containing the pulse was usually followed by a shortened tI. Positive pulses did not significantly effect the duration of tI. Regardless of sign of pulse tI was not usually changed but occasional large shortening occured in subsequent breaths before and after P.S.R. block.

This indicates that the tE containing the stimulation is governed by a balance between P.S.R. and R.A.R. activity. The tI following the stimulus is governed by a balance between "memory" of P.S.R. and R.A.R. activity. In the breaths following both tE and tI were influenced by "memory" of R.A.R. activity only. However "memory" of strong R.A.R. activity is required to affect tI.

During this study it was intended to use phenyldiguanide (P.D.G.) to test J receptor patency. Intravenous injections of P.D.G. have been used to provoke respiratory reflexes, these have been considered to be due mainly to stimulation of type J receptors. However although most workers demonstrated that vagotomy abolished or reduced these reflexes, some still had significant response

to P.D.G. after vagotomy. A study was conducted to resolve this difference and demonstrate the sites at which P.D.G. acts in rabbits.

We measured tE and tI in 10 anaesthetized spontaneously breathing rabbits. 50 μg/kg P.D.G. was given intravenously (via a catheter with its tip close to the right atrium) to the intact rabbit; after blocking epicardial receptors; immediately after bilateral cervical vagotomy; 15 minutes after vagotomy; and after the glossopharyngeal nerves were cut near the base of the skull.

The respiratory reflex after injection of xylocaine, 15 minutes after vagotomy, and after cutting the glossopharyngeal nerves was as pronounced as in the intact state, and consisted of an increase in frequency almost totally due to a reduction in tE. With injections given up to 3 minutes after bilateral vagotomy the respiratory response was greatly attenuated and variable. We suggest this question of timing may contribute to the differences seen by different groups of workers. It is clear that intravenous injection of P.D.G. is not an adequate test of J receptor presence in the rabbit.

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# INTRODUCTION

The introduction will review the material relevant to vagal influences on respiratory pattern. Firstly the control of breathing will be briefly reviewed in terms of:

1) central control,
2) efferent activity,
3) afferent activity.

Then the vagal influence of pulmonary receptors will be examined more closely in terms of:

1) non myelinated fibres,
2) slowly adapting receptors with myelinated fibres,
3) rapidly adapting receptors with myelinated fibres.

Next the regulation of duration of inspiration and expiration will be discussed. Then the evidence for linking of respiratory cycles will be examined. And finally a review of the conflicts in the literature on the effects of phenyldiguanide will be made.

## CONTROL OF BREATHING

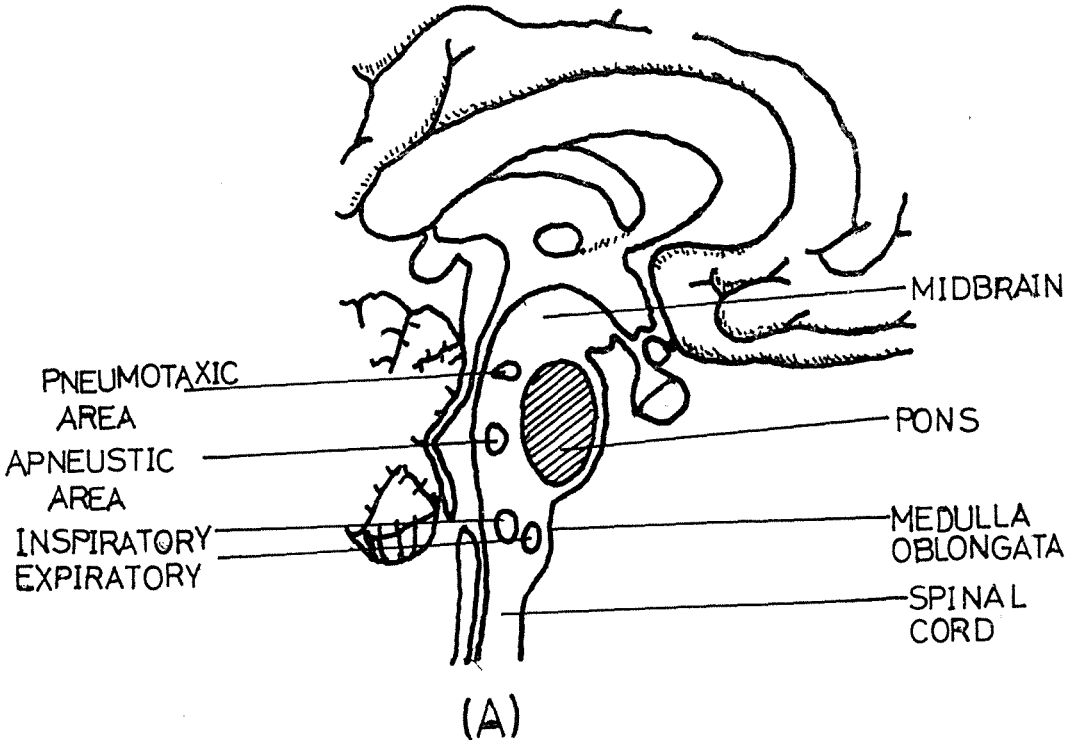
It is easy to take breathing for granted, we breathe approximately 16 times a minute without much thought until we over exert ourselves. And yet the pattern of breathing changes all the time

to keep maximum efficency despite altered oxygen needs and CO2 production with different activities.

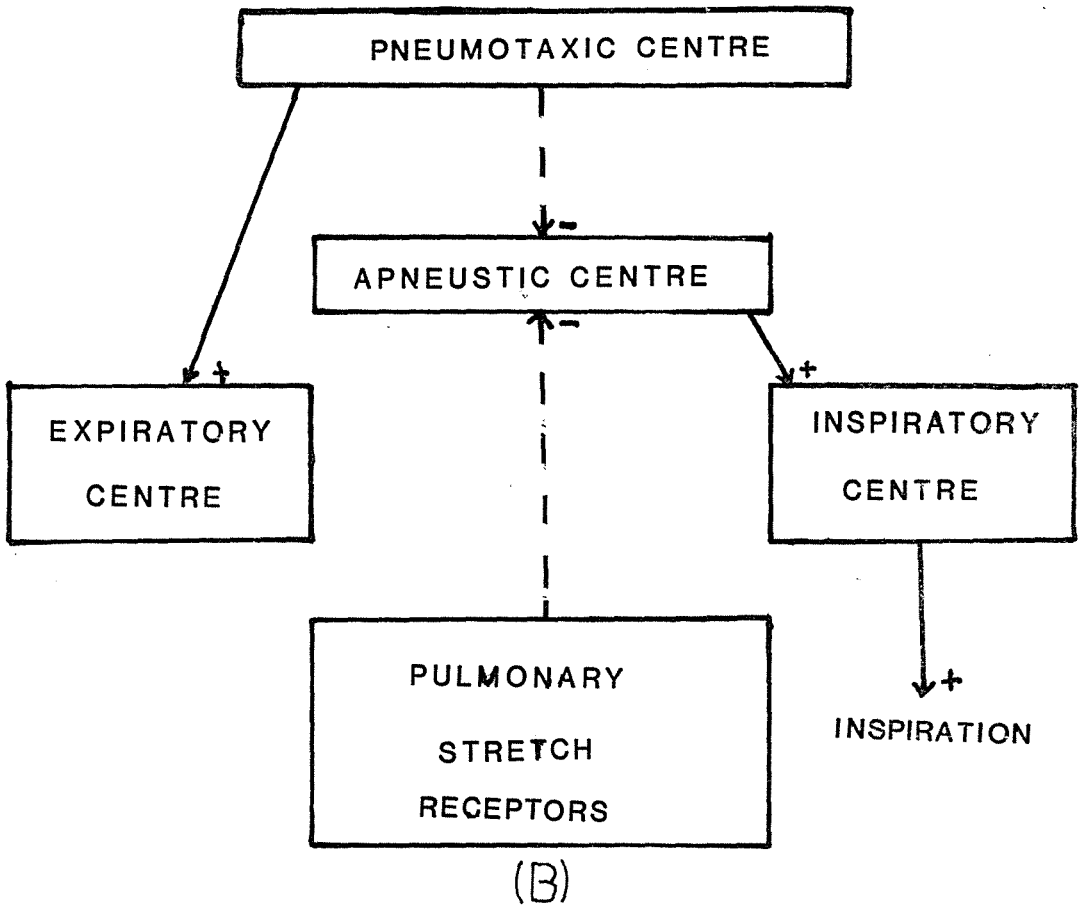
These changes in pattern are brought about by changes in the brainstem "respiratory centres" neural activity affecting efferent activity to the respiratory muscles. These changes are made in response to afferent information from receptors, located mainly in the thorax.

Central control

In 1812 LeGallois reported that if the medulla oblongata is isolated, cells within continue to generate a respiratory rhythm. Thus the medulla contains a respiratory pattern generator. Since Flourens 1851 described a "vital node" the concept of a small, bilateral, inherently rythmic centre has remained attractive. From early attempts to localize this centre this pattern generator was historically described as the "respiratory centres" (fig 1). These consisted of the inspiratory and expiratory centres which provided the oscillations from inspiration to expiration. The pattern from these was thought to be modified by the pneumotaxic centre which recieved vagal afferent information and the inhibitory apneustic centre. The pneumotaxic centre was considered to receive information on the onset of inspiration. After a delay on receiving this information the pneumotaxic centre was considered to inhibit the inspiratory




(A)




(B)

FIG 1. SCHEMATIC REPRESENTATION OF THE LOCATION (A) AND INFLUENCES (B) OF THE HISTORICAL "RESPIRATORY CENTRES".

FACILITATORY INFLUENCE

INHIBITORY INFLUENCE

neurons and terminate inspiration.

Pitts, Magoun & Ranson 1939 described the anatomical localization of overlapping inspiratory and expiratory neurons, dispelling the concept of discrete centres. Thus this concept of "respiratory centres" must now be redefined as a group of neuronsand synapses that influence the pattern of breathing. Cohen (1970 & 1976) proposed a model of interacting neuron systems which has replaced this model. This model differs from the historical mainly by describing functional rather than anatomical centres. Hence reference to the "respiratory centres" will refer to all the central neuron systems concerned with generating respiratory pattern.

Pitts (1946) considered the "respiratory centres" contain linked inspiratory neurons and linked expiratory neurons which synchronizes their activity. These inspiratory and expiratory neurons are mutually inhibitory which limits duration of activity during eupnoea (Comroe 1975). Although the expiratory neuron pool is active , in eupnoea this activity does not reach the threshold needed to activate expiratory motor neurons and therefore expiratory muscles. Thus in eupnoea expiration is passive (Comroe 1975). The "respiratory centres" may consist of inhibitory interaction between two groups of neurons to generate rhythm (Robson). This is a persistant idea with little evidence for it

(Mitchell & Berger 1975).

A model of the "respiratory centres" was proposed (von Euler & Trippenbach 1976; von Euler 1977; Cohen & Feldman 1977) consisting of functional pools of neurons generating the rhythm (fig 2). A pool of neurons generate the central inspiratory activity (CIA) which produces the basic pattern. This is terminated by another pool of neurons the inspiratory off-switch (O-S). A third pool of neurons is responsible for the interaction between the CIA pool and the activity from the pulmonary stretch receptors (P.S.R.). Once this pool reaches a threshold level of activity the O-S activity may rise quickly to terminate inspiration and CIA. The activity of the CIA-P.S.R. pool will die slowly with slow reduction of P.S.R. activity. Another pool of neurons may control rate of breathing with inspiratory and expiratory duration controlled by different sections of this pool. The inspiratory rate being inhibited by P.S.R. activity and the expiratory rate facilitating O-S activity.

All these pools are modified by afferent information (Trippenbach & Milic-emili 1977). The way in which afferent information modifies the "respiratory centres" will be discussed later. The CIA generator has efferents to the spinal respiratory motor neurons.

Efferent systems

The diaphragm is activated during inspiration

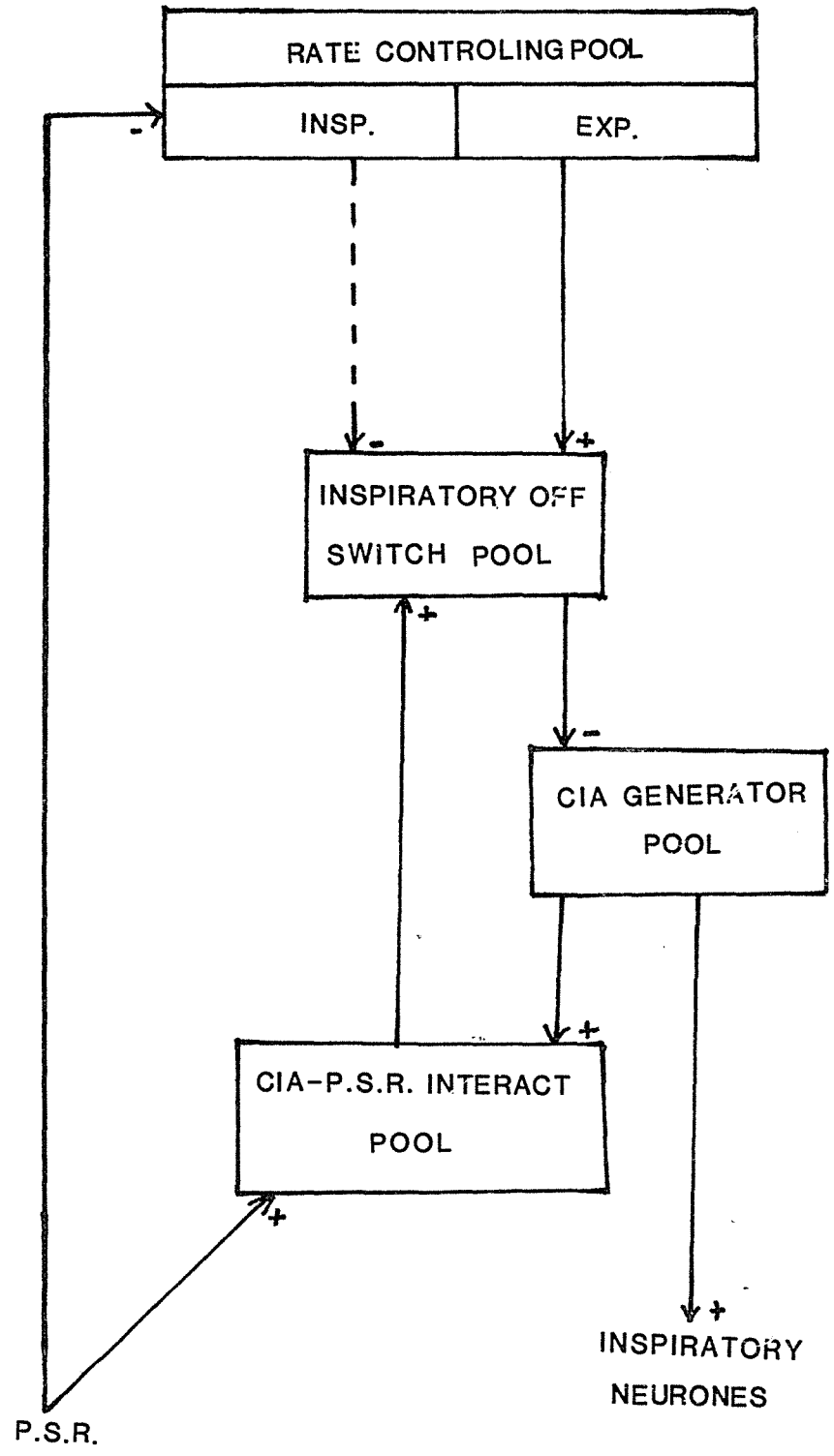



FIG 2. SCHEMATIC REPRESENTATION OF THE POOLS OF NEURONS FORMING THE CENTRAL CONTROL OF RESPIRATION.

+ → FACILITATORY

− → INHIBITORY

– – → ALTERNATIVES

by the phrenic nerve with neurons arising from cervical nerves C3, 4, and 5. These are efferents from the "rhythm generator" and are the only fibres in the phrenic nerve. The diaphragm has few muscle spindles thus the phrenic nerve is almost exclusively the source of diaphragmatic activity. The fibres of the phrenic nerve lack Renshaw cells with inhibitory feedback to prevent after discharge (Widdicmbe & Davies 1983).

Thus a recording of phrenic activity (fig 3) shows an accurate representation of the drive to inspire from the "respiratory centres", although some after discharge is seen. A recording of diapragmatic emg also records this drive to inspire. A trace of phrenic activity or diaphragmatic emg shows activity during inspiration and no activity during expiration.

The "respiratory centres" have efferent fibres to the other respiratory muscles, external and internal intercostal and abdominal muscles. However these muscles also have muscle spindles which produce reflex contraction (Widdicombe & Davies 1983).

Afferent systems

A major afferent influence on respiratory pattern is from chemoreceptors (fig 4). The main peripheral chemoreceptors are located in the carotid bodies and aortic bodies with afferents in

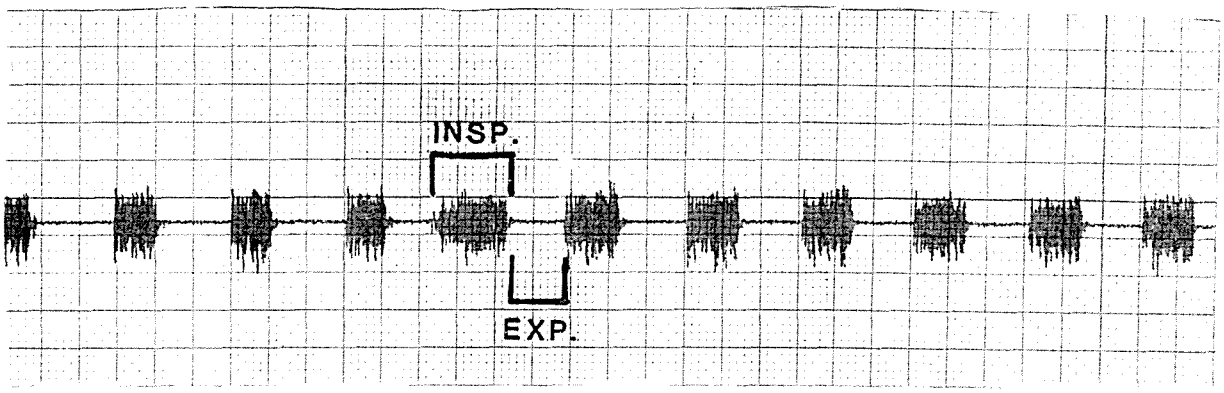



FIG 3. TRACE OF PHRENIC ACTIVITY.

INSP. SHOWS ACTIVITY OF PHRENIC DURING INSPIRATION ($T_I$).

EXP. SHOWS LACK OF PHRENIC ACTIVITY DURING EXPIRATION ($T_E$).

the glossopharyngeal and vagus nerves respectively. These receptors are stimulated by low arterial oxygen tension and increased levels of CO2 (Comroe 1975). However Guz, Noble, Widdicombe, Trenchard & Mushin 1966 showed block of these receptors did not influence pattern of breathing in eupnoea.

The central chemoreceptors are stimulated by an increase in hydrogen ion concentration in the cerebral spinal fluid. Hydrogen ion levels in the cerebral spinal fluid are related to CO2 levels. Thus stimulation of central chemoreceptors is due to raised levels of CO2 in the general circulation (Comroe 1975).

Stimulation of chemoreceptors increase frequency of breathing by inhibiting the inspiratory O-S pool of neurons and facilitating the CIA generator (von Euler 1977). There is a latency of 20-30 seconds after increasing CO2 levels before much change in breathing is seen and it may be 5-10 minutes before a new level of respiration is set (Widdicombe & Davies 1983). This illustrates that chemoreceptors have a long term influence on the pattern of breathing.

The pulmonary receptors, pulmonary stretch receptors (P.S.R.) and rapidly adapting receptors (R.A.R.), of the myelinated fibres of the vagus nerves are most important for breath by breath control of pattern of breathing. The R.A.R. are stimulated by inflation and deflation of the lungs

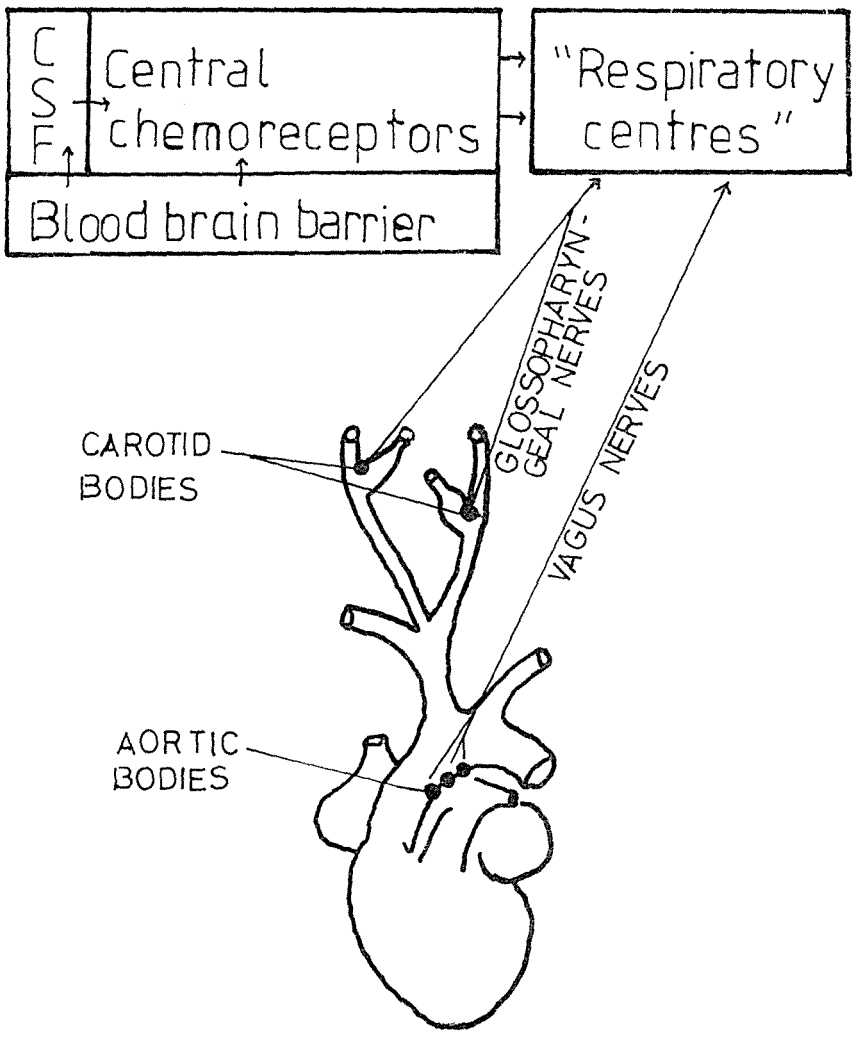



FIG 4. THE CHEMORECEPTORS.

to increase frequency of breathing (Widdicombe & Davies 1983). This is probably by stimulating the inspiratory O-S (von Euler 1977). Augmented breaths or sighs are also caused by R.A.R. stimulation (Davies & Roumy 1976), by large lung inflations and is probably by inhibition of the inspiratory O-S pool of neurons or by facilitating the inspiratory rate controlling pool (von Euler 1976).

The P.S.R. are stimulated by inflation of the lungs to terminate inspiration and initiate expiration (Widdicombe & Davies 1983). This is probably by interacting with the CIA-P.S.R. interaction pool of neurons to facillitate the O-S and by inhibition of the insiratory rate controlling pool (von Euler 1976).

The type J receptors (JR) have mainly nonmyelinated vagal fibres and are stimulated physiologically by pulmonary oedema to cause an increase in frequency of breathing (Paintal 1977). Their effect on the "respiratory centres" has not been established.

In unanaesthetized animals emotion and voluntary control may influence respiratory pattern. Voluntary control probably bypasses the respiratory centres and exerts its effect directly on the respiratory muscles (Widdicombe & Davies 1983). Emotion may influence the rate controlling pool in the pons (von Euler 1977).

Propioreceptors in the chest wall relay information about the position of the chest and allows efficient breathing regardless of body position. Activity from these fibres facillitate either the O-S pool or the CIA-P.S.R. interaction pool, thus shortening inspiration (von Euler 1977).

Hyperthermia affects the rate and growth of CIA and thus influences the CIA generator. It also interacts with the CIA-P.S.R. pool to activate the O-S (von Euler 1977).

Fig 5 is a diagragm of the afferent influences on the "respiratory centres".

## PULMONARY RECEPTORS

The pulmonary receptors consist of type J receptors with nonmyelinatewd fibres, R.A.R.with myelinated fibres, P.S.R. which adapt slowly and have myelinated fibres (Paintal 1973b). In the cat there are 4 times as many non myelinated fibres as myelinated fibres from P.S.R. and R.A.R.(Agostoni, Chinnock, Daly & Murray 1957). The P.S.R. and R.A.R.are particularly important in breath by breath control of breathing, and help maintain an efficient breathing pattern.

### Receptors of non myelinated fibres

The regenerative region of nerve fibres myelinated or not are not protected by the diffusion barrier of the nerve sheath (Paintal

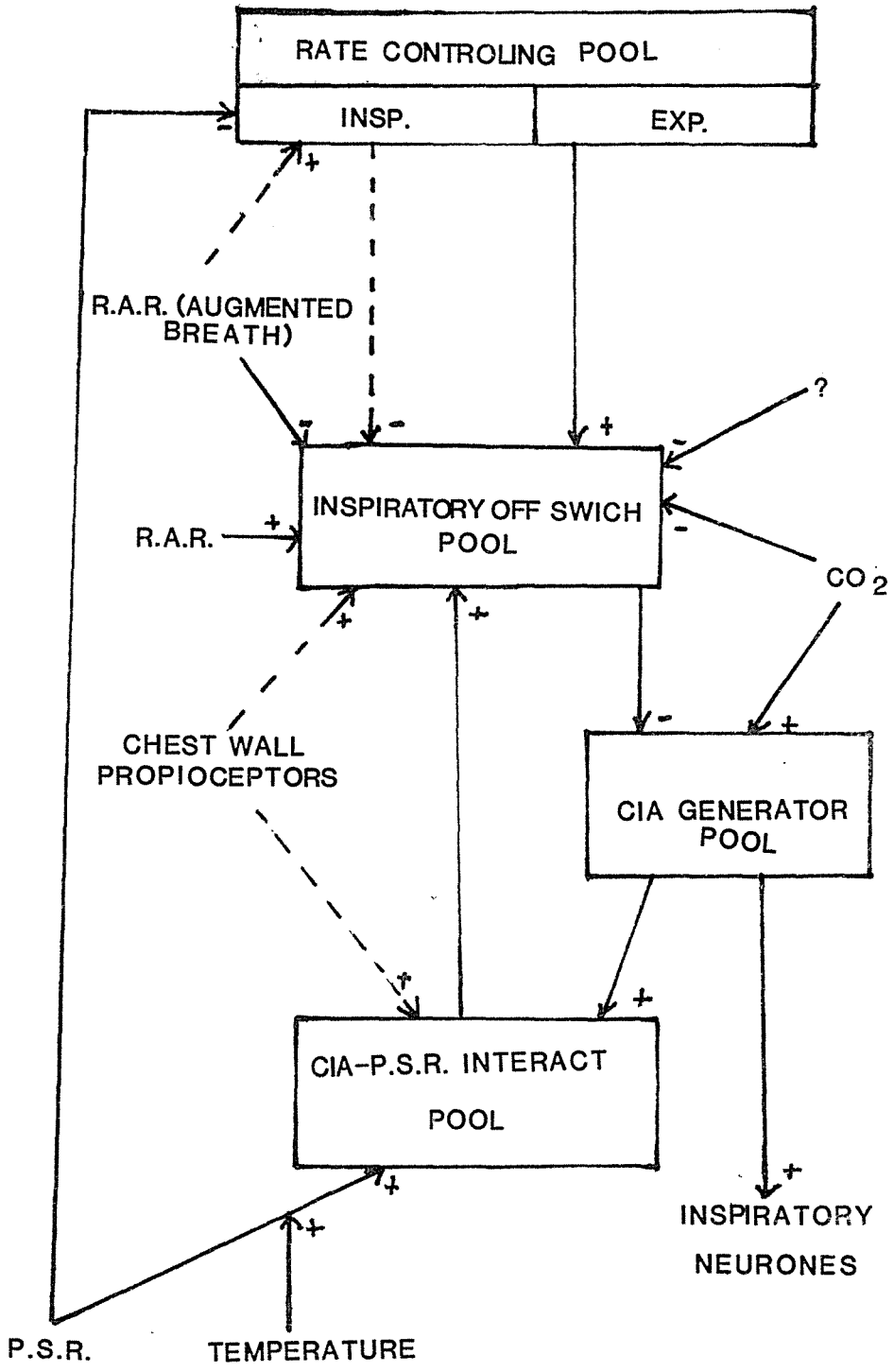



FIG 5. AFFERENT PATHWAYS TO THE "RESPIRATORY CENTRES".

+ FACILITATORY

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ALTERNATIVES

1973b). Thus some chemical types of chemical are able to stimulate or sensitize at this region examples of these are volatile anaesthetics and veratrum. Non myelinated fibres are susceptible to stimulation by a wider variety of drugs than myelinated fibres as the regenerative region is not protected by a myelin sheath (fig6). Acetylcholine, 5-hydroxytryptamine, phenyldiguanide, histamine and similar chemicals may only stimulate non myelinated fibres (Paintal 1973b).

Type J receptors were discovered accidentally while studying other nonmyelinated fibres using P.D.G. as a stimulant (Paintal 1953, 1954, 1973a). It was some time after discovery that the physiological stimulus of these receptors became known. Initially interest focussed on their response to forced deflation and collapse of the lung and hence were known as deflation receptors (Paintal 1973a). Sellick and Widdicombe 1970 found although most receptors were not stimulated by lung inflations or deflations some were stimulated by deflation produced by 50 ml pneumothorax.

Eventually it became known that these receptors were stimulated by pulmonary oedema, specifically the increase in interstitial volume consequent of rise in pulmonary capillary pressure (Paintal 1969). In keeping with this function it has been shown they lie close to the pulmonary

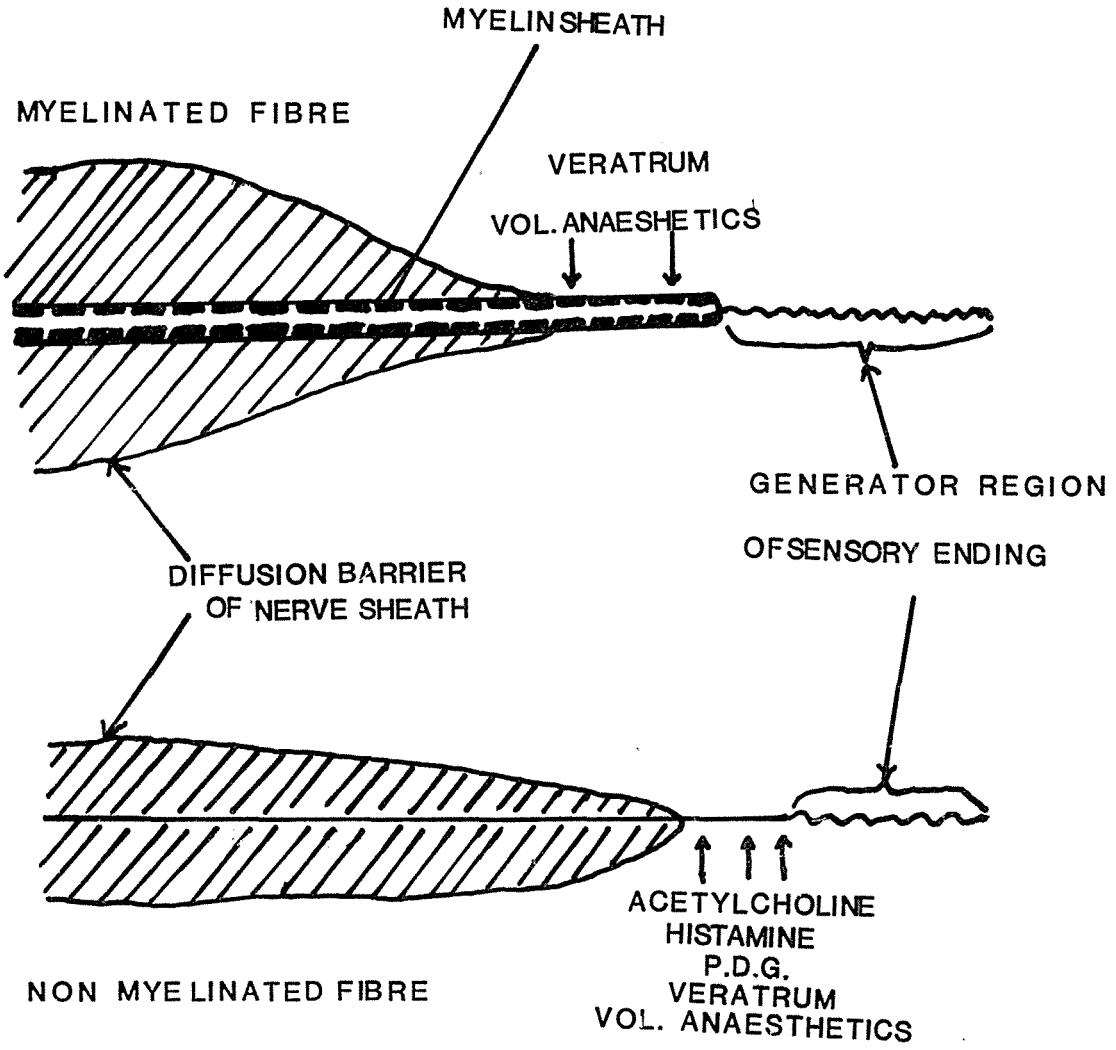


FIG 6. SCHEMATIC DIAGRAM OF MYELINATED AND NON MYELINATED FIBRES SHOWING THE RESPONSE TO CHEMICAL STIMULATION.

capillaries, giving rise to the name juxtapulmonary capillary receptors or type J receptors (Paintal 1973a).

Stimulation of J receptors accelerates breathing, and sometimes causes apnoea. It also causes hypotension, bradycardia and inhibition of somatic muscles (Paintal 1970, 1973b). Type J receptors are probably stimulated physiologically by a rise in pulmonary capillary pressure due to exercise. This may contribute to the acceleration of breathing and may be involved in the sensations of breathlessness (Paintal 1973a).

Substances such as 5-hydroxytryptamine stimulate these endings and as such may stimulate J receptors when released by pulmonary embolism. Other pathological conditions involving pulmonary circulation, suh as pulmonary oedema and embolism, stimulate J receptors, resulting in tachypnoea (Guz & Trenchard 1971). Sensations of dyspnoea in these diseases may be produced by J receptor stimulation (Paintal 1973a).

Slowly adapting receptors

Breuer and Hering in 1868 noted that inflation of the lungs in inspiration terminated inspiration while deflation terminated expiration, initiating inspiration. This effect was abolished by vagotomy. Breuer and Hering proposed that receptors which detected the state of the lung distension lay in

the lung tissue with the vagus as an afferent to the respiratory centres. They proposed that the respiratory centre which produced the normal respiratory pattern required vagal information about the state of the lung.

Adrian (1933) showed that when a sudden and maintained inflation is applied to the lungs, one type of vagal fibre discharges, the receptor of this fibre became known as the pulmonary stretch receptor. Davis, Fowler and Lambert (1956) suggested stretch from lung inflation was the primary stimulus with some responsiveness to the rate of change of stretch. Physiological and degeneration experiments along with histological evidence indicates they are located in the smooth muscle of the bronchi (Widdicombe 1954b). It has been noted these receptors are either slowly adapting or have varying adaption rates (Widdicombe & Davies 1983).

The main influence of P.S.R. is to shorten duration of inspiration accompanied by reduced tidal volume and lengthened duration of expiration (Widdicombe & Davies 1983). The P.S.R. are stimulated during the lung inflation of inspiration and activity rises till the O-S mechanism is activated, thus terminating inspiration (von Euler 1977). During the first part of expiration while the lungs are deflating, these receptors are still strongly active but discharge reduces as lungs empty (Widdicombe and Davies 1983). P.S.R. are

stimulated proportionally by mechanical deformation caused by transpulmonary pressure (Davis, Fowler, and Lambert 1956).

The inflation reflex exists in all mammals and operates qualitatively in the same manner in all of them. The strength of the reflex varies considerably, being strongest in rabbits and weakest in man (Widdicombe 1961). Since rhythmical breathing continues after bilateral vagotomy, the activity of lung stretch recetors is not essential for rhythm but modify the pattern. The advantage of this modification is to make breathing more efficient.

Although some receptors have superimposed cardiac rhythm (Paintal 1933) this is likely to be due to influence from local vessels rather than functional. This is supported by the observation that no cardiac rhythm is observed in these receptors when stimulated by inflation (Paintal 1973a). Recently it has been shown that P.S.R. can be inhibited by airway CO2 (Coleridge, Coleridge, & Banzett 1978), hypoxia does not similarly affect P.S.R. activity. P.S.R. also causes reflex bronchodilation, systemic vasodilation, tachycardia, and widening of the glottal apperture (Widdicombe 1982).

Rapidly adapting receptors

Impulses from endings which adapted rapidly to

maintained inflation or deflation of the lungs were recorded by Knowlton and Larrabee 1946. These endings were called rapidly adapting receptors. Widdicombe 1954a located many of these receptors in the trachea. Further investigation revealed endings in intrapulmonary airways (Mills, Sellick, & Widdicombe 1970) which lie beneath the respiratory tract epithelia. These have similar responses to those in the trachea. These endings have been named irritant receptors. The greatest concentration of these receptors are in the large airways (Sant'Ambrogio 1982).

There is much debate on the naming of these receptors. Although a natural stimulus to these receptors may be mechanical irritation, these receptors also play a role in determining pattern of breathing. I consider the term rapidly adapting receptor more appropriate in terms of their response to stimulus, I will thus refer to them as rapidly adapting receptors.

The physiological properties of extrapulmonary and intrapulmonary rapidly adapting receptors is identical (Paintal 1973a). In the cat R.A.R.are silent during eupnoea (Widdicombe 1954a, Knowlton & Larrabee 1946), even during moderate increase in tidal volume, while in the rabbit, R.A.R.show activity during spontaneous respiration (Sellick & Widdicombe 1970). Activity in the rabbit usually consists of a brief burst near the peak inspiration

(Sellick & Widdicombe 1970). Davies and Roumy 1982 recording R.A.R.activity, recorded greatest stimulation by deflation at functional reserve capacity and by deflation at peak tidal volume.

Stimulation of these receptors may cause tachypnoea, mainly shortening expiration

(Widdicombe & Davies 1983) and may shorten inspiration (Widdicombe & Winning 1976). The augmented breath may be initiated by stimulation of R.A.R.(Davies & Roumy 1982). Reflex bronchial and laryngeal constrictions are also seen. R.A.R.are stimulated by inflation and deflation, mechanical irritation (Widdicombe & Davies 1983), chemical irritation (Karczewski & Widdicombe 1969a) and some lung diseases, such as pneumonia, oedema and embolism (Mills, Sellick & Widdicombe 1969; Frankstein & Sergeeva 1966; Frankstein 1970).

## REGULATION OF THE PHASES OF BREATHING

Clark and von Euler (1972) proposed that duration of inspiration was regulated by two mechanisms. At tidal volumes below the threshold for the Hering-Breuer reflex, duration of inspiration is governed by a central mechanism, thus holds a constant relationship with tidal volumes. The range of volumes at which this mechanism operates is called range 1. Duration of

inspiration becomes dependant on lung volume at tidal volumes above this threshold, at thse tidal volumes duration of inspiration has a hyperbolic relationship with tidal volume. The range of volumes over which this relationship holds is called range 2 (fig 7).

In humans, having a high threshold for the Hering-Breuer reflex there is a distinction between the two ranges. In laboratory animals, having a lower threshold for the Hering-Breuer reflex the two ranges merge, shown in the cat (Clark & von Euler 1972) and rat (Cragg & Drysdale 1983). This in terms of von Eulers model suggests that where two ranges exist, duration of inspiration is governed by CIA alone in range 1, P.S.R. activity and CIA govern durat-ion of inspiration in range 2. However in animals in which the two ranges merge tI is governed by P.S.R. and CIA activity.

Inspiration is initiated by P.S.R. (Paintal 1973a) and probably also by R.A.R.(Davies, Sant'Ambrogio, Sant'Ambrogio 1981). Termination of inspiration probably involves R.A.R.as well as P.S.R. (Davies, Nadal & Weinmann 1984) Pressure pulses of inflation and deflation influence the duration of inspiration by the activity of P.S.R. (Paintal 1973a). Activity of R.A.R.may be involved in the augmented breath. Augmented breaths are extra large lung inflations and may be involved in preventing local lung collapse during normal

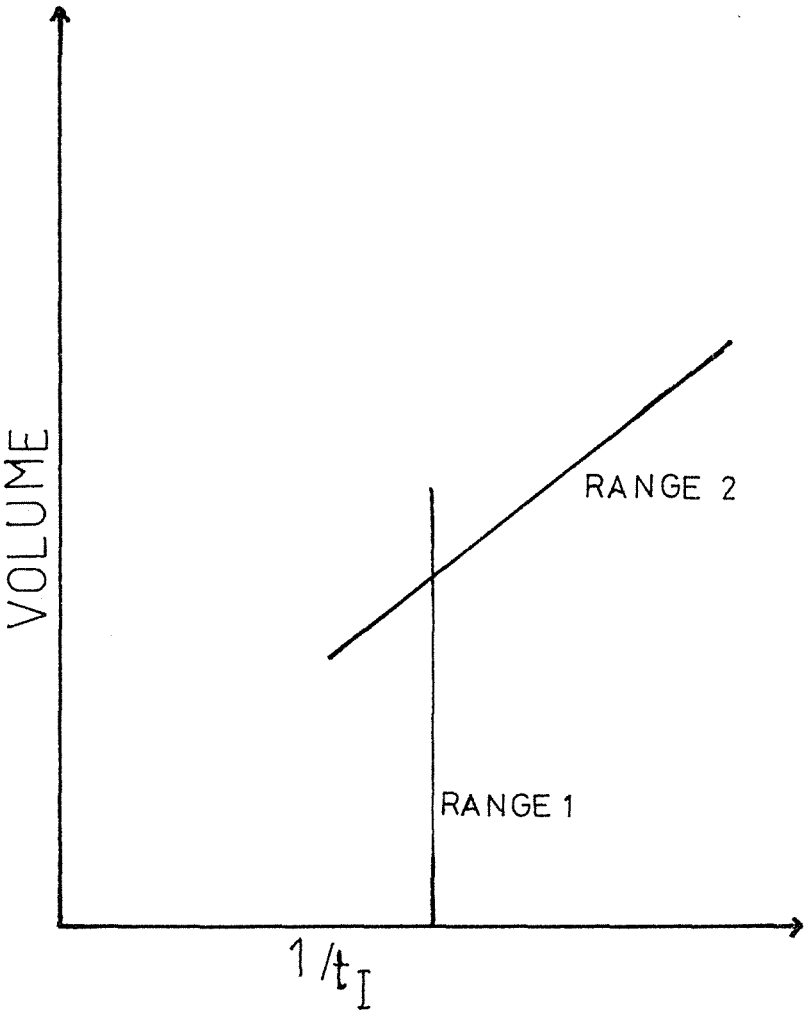


FIG 7. THE RELATIONSHIP BETWEEN VOLUME AND DURATION OF INSPIRATION IS CONSTANT IN RANE1 BUT HYPERBOLIC IN RANGE2.