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OF PULMONARY RAPIDLY ADAPTING RECEPTORS

by

JUN YU
from the People's Republic of China, April 1987

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

PHYSIOLOGY

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA

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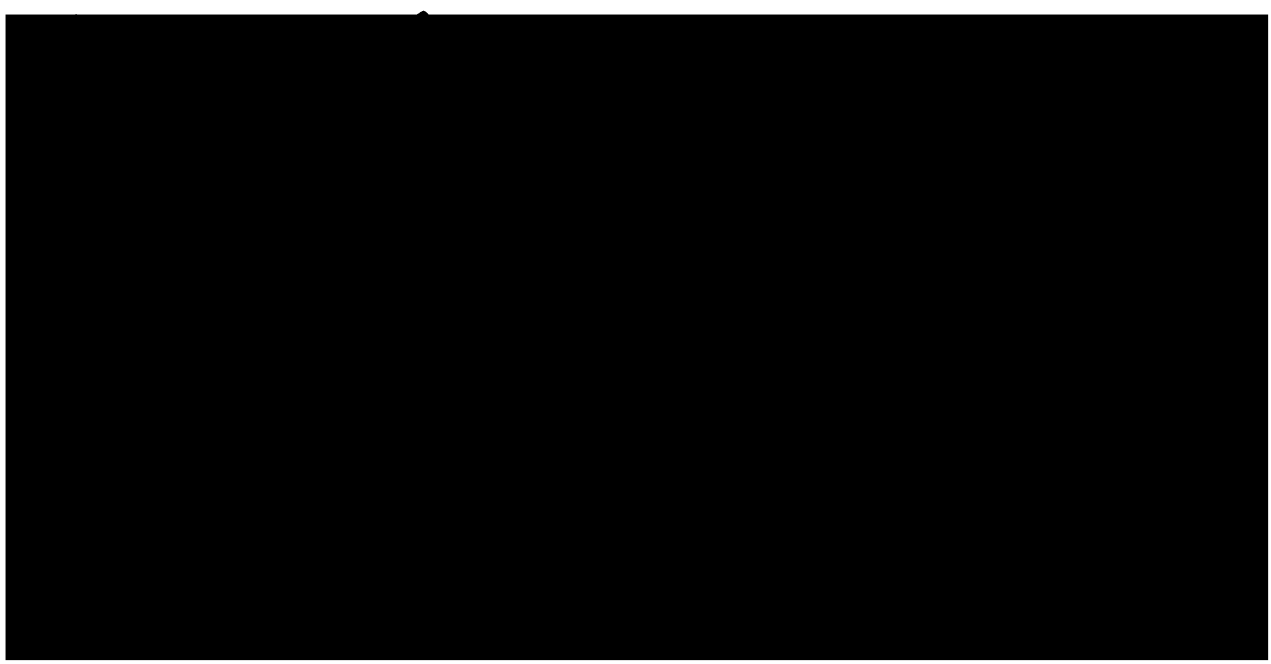

Dedicated to

my parents

Zhu, Yu and Yu, Zhi-yuan

for their love, support, and education to their children.

my wife, Zheng, Jing-juan

for her love, understanding, and encouragement.

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I also would like to thank Drs. Harold Schultz and Thomas Pisarri and Mr. Albert Dangel and Mr. Ronald Brown for their help.

AFFERENT PROPERTIES AND PHYSIOLOGICAL FUNCTIONS OF PULMONARY RAPIDLY ADAPTING RECEPTORS

Yu, Jun April 1987

Abstract of a doctoral dissertation at
the University of California, San Francisco

Dissertation supervised by Professor John C.G. Coleridge

Rapidly adapting receptors (RARs) are reported to be inactive in quiet breathing, but to become active when airflow increases and when the lungs become stiffer in pulmonary disease. The purpose of this study is to determine whether RARs in normal lungs sense small changes in dynamic lung compliance (C_{DYN}), to compare the effects of C_{DYN} on RARs and slowly adapting pulmonary stretch receptors (PSRs), and to examine some of the reflex effects of RARs.

In anesthetized cats and rabbits, activity of RARs and PSRs was recorded from the cervical vagus nerves. The lungs were ventilated at constant tidal volume and frequency from an end-expiratory pressure (PEEP) of 3-4 cm H_2O. C_{DYN} was increased to maximum by hyperinflation, and then decreased in steps of approximately 10% to about 60% of maximum by periodically removing and then restoring PEEP. At maximal C_{DYN}, RARs discharged irregularly, averaging 1 impulse/sec; when C_{DYN} was reduced, activity increased significantly; when C_{DYN} was restored, activity returned to control. By contrast,

when C_{DYN} was reduced to 60% of maximum, mean PSR discharge did not change. For equivalent increases in transpulmonary pressure RARs were stimulated more effectively by reduced C_{DYN} than by increased tidal airflow. By contrast PSRs were sensitive mainly to tidal volume.

To determine if tonic input from RARs influenced respiratory pattern, the vagus nerves were cooled gradually in spontaneously breathing rabbits. Cooling to 10°C blocked the Hering-Breuer reflex, and significantly increased inspiratory time (Ti), but did not change expiratory time (Te). Cooling from 10 to 5°C significantly increased Te: this increase was probably due to removal of RAR input.

To determine whether stimulation of RARs evokes secretion by airway submucosal glands, tracheal secretion was measured in anesthetized, artificially-ventilated dogs by the 'hillocks' method. Three maneuvers (application of negative end-expiratory pressure, removal of PEEP and reduction of C_{DYN}) which stimulate RARs increased tracheal secretion without any corresponding change in blood gas tensions. Responses were abolished by cooling the cervical vagus nerves to 6°C.

It is concluded that under normal circumstances RARs supply information regarding the force required to expand the lung and that they shorten Te, and when stimulated they increase airway secretion.

John Colebridge

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INTRODUCTION

Histological studies of the vagus nerve and its branches in cats reveal that some 10,000 afferent fibers are distributed to the lungs and lower airways (Agostoni et al, 1957). These vagal afferent fibers are generally believed to arise from three different types of receptors. These are: slowly adapting pulmonary stretch receptors (PSRs); rapidly adapting receptors (RARs); and the endings of pulmonary and bronchial C-fibers. The first two receptor types are supplied by myelinated (A) fibers, while C-fibers are nonmyelinated.

C-fibers account for four fifths of the total number of vagal afferents (Agostoni et al, 1957), and are stimulated by a wide variety of chemicals. The afferent properties and physiological functions of C-fibers have been extensively dealt with in a recent review (Coleridge and Coleridge, 1984).

The remaining 2,000 myelinated A fibers provide information about stretch of the lung to the respiratory center of the medulla. The diameters of these fibers range from 1 to 10 μm and their conduction velocities range from about 5 to 60 m/sec (Sampson, 1977; Paintal, 1973). Usually the fibers supplying PSRs have somewhat larger diameters and

faster conduction velocities than those supplying RARs, though there is overlap (Paintal, 1973; Sampson, 1977). In action potential studies, PSRs and RARs can be easily distinguished by the pattern of their afferent response to lung inflation, as their name suggests.

PSRs are stimulated by inflation of the lung and by the rate of volume change. The phasic action of the reflex is to cut short inspiration and thus to control inspiratory time (Ti) and tidal volume (Knox, 1973). The strength of the inflation reflex is usually tested by determining the length of apnoea produced by lung inflation. In addition, tonic activity in PSRs in the expiratory pause is thought (Knox, 1973; Trenchard, 1977) to determine expiratory time (Te). Hence PSRs are often thought to be the only receptors concerned in the vagal control of respiratory pattern under normal conditions (Bradley, 1977). The transduction properties and reflex effects of PSRs have been reviewed recently (Pack, 1981; Sant'Ambrogio, 1982; Coleridge and Coleridge, 1986).

RARs have been studied for more than four decades, but their physiological function is still debatable. Calculated from the relatively unbiased estimate of the incidence of RARs and SARs in cats (Knowlton and Larrabee, 1946), about 40% of myelinated fibers are rapidly adapting. In

other words, in cats there are about 800 fibers arising from RARs. Therefore, it would certainly be interesting to learn how the numerous RARs are stimulated and to identify their reflex functions. In this chapter I shall describe what is already known about RARs from the work of others, what research I am going to do and why I am going to do it. First, however, I shall describe in some detail the classical study by Knowlton and Larrabee (1946), which is important, because these results are still held as a fundamental framework for understanding the afferent properties of RARs.

In Adrian's classic study of slowly adapting stretch receptors in the lung (1933), he briefly described a second group of lung mechanoreceptors stimulated by forced deflation, whose discharge adapted rapidly. Knowlton and Larrabee (1946) were the first to describe the response of receptors of this type to lung inflation, and to make a careful comparison of their properties with those of PSRs. Knowlton and Larrabee distinguished PSRs and RARs in the lungs in terms of an arbitrarily defined 'Adaptation Index'. They stimulated RARs by injecting a known volume of air into the lung, and measured the subsequent percentage decline in frequency over a fixed interval of time during a maintained inflation according to the following formula

Adaptation index

$$= \frac{\text{peak f - average f during 2nd sec of inflation}}{\text{peak f}} \times 100\%$$

In their original paper, Knowlton and Larrabee did not indicate whether the second sec of inflation was measured from the begining or the end of inflation, or from the point of peak frequency. Several years later, Widdicombe (1954 b) defined this measurement as starting from the point of peak frequency.

Typically, PSRs have an adaptation index of less than 55%, whereas RARs have an index greater than 80%. Knowlton and Larrabee (1946) and Widdicombe (1954 b) found a small percentage of fibers (about 8%) whose adaptation index was between these two extremes. These were termed intermediate receptors. RARs in this intermediate range are easy to identify, because in contrast with PSRs, their firing pattern during maintained inflation is irregular, and often consists of scattered impulses with each cardiac cycle. This irregularity of firing pattern in response to a steady-state stimulus is consistent with what is known about the discharge characteristics of rapidly adapting mechanoreceptors in other tissues. As Adrian (1933) described, and Knowlton and Larrabee

(1946) and Widdicombe (1954 b) confirmed, RARs are strongly stimulated by forced deflation of the lungs.

Because RARs were found to have a much higher threshold to inflation than PSRs, Knowlton and Larrabee did not think that RARs played any part in determining the pattern of eupneic breathing. They believed that these receptors were not recruited unless the depth of inspiration increased. This opinion is still widely held and often repeated (Mills et al, 1969; Pack and Delaney, 1983).

Slowly and rapidly adapting receptors are present in many structures, for example, the Type I and Type II mechanoreceptors of hairy skin (Burgess and Perl, 1973). When a constant distorting force is applied to a slowly adapting receptor it fires with a regular frequency that relates linearly to the force applied. When a constant distorting force is applied to a rapidly adapting receptor it fires initially with a high frequency, but its firing rate decays rapidly with time, often to a small fraction of its initial frequency, and the persisting discharge is characteristically irregular. The characteristics of slowly and rapidly adapting mechanoreceptors have been studied most completely in the crayfish stretch receptor organ where these two types of mechanoreceptors occur in pairs, and where the nerve cells are large, and close to the sensory terminals (Florey and

Florey, 1955). Studies of crayfish stretch receptors indicate that the visco-elastic coupling of the sensory terminal to the surrounding tissue largely determines the adaptation characteristics (Eyzaguirre and Kuffler, 1955; Krnjevic and Van Gelder, 1961).

NOMENCLATURE

Since first identified by Knowlton and Larrabee (1946), rapidly adapting receptors have been given several names based on the different methods used by the investigators to study their properties. They have been termed 'deflation receptors', 'cough receptors', 'pulmonary flow receptors' and 'irritant receptors'. These multiple terms caused enormous confusion for many years, However, the term 'rapidly adapting receptors' is now used by most investigators.

The term 'deflation receptors' has been used in rabbits to describe receptors that are stimulated by forced deflation (Koller and Ferrer, 1970; Roumy and Leitner, 1980) and now are thought to be identical with RARs. 'Deflation receptors' do not fully describe RARs response, and the term is particularly confusing because it has been applied to the pulmonary endings of unmyelinated fibers (Paintal, 1973).

The term 'cough receptors' is applied to a particular

group of RARs concentrated at the carina and major bronchi; stimulation of these receptors gives rise to cough (Widdicombe, 1954 a). On the other hand, RARs located in the intrapulmonary airways are thought not to evoke cough (Mills et al, 1969).

'Pulmonary flow receptors' were named by Sullivan and Read (1975) because they observed a positive correlation between RAR activity and tracheal airflow, and believed that these receptors sensed airflow.

'Irritant receptor' was the name given by Widdicombe and his coworkers, who observed that RARs in rabbits were not only stimulated during pathological conditions in the lungs, such as those produced by pneumothorax, atelectasis, anaphylaxis, pulmonary congestion and microembolism, but also responded to inhalation of chemical irritants (such as ethyl ether, ammonia vapour and cigarette smoke), and mechanical irritants (such as 'inert' carbon dust and the passage of an endobronchial catheter) (Mills et al, 1969; Sellick and Widdicombe, 1969; Sellick and Widdicombe, 1971; Widdicombe, 1974). These observations, and the observation that RARs appeared to have little or no activity in eupnea (Knowlton and Larrabee, 1946; Sellick and Widdicombe, 1969; Bergren and Sampson, 1982) prompted Widdicombe and his coworkers to conclude that the essential property of RARs

was their response to irritant conditions of the airways; and for this reason they called them irritant receptors.

The term 'irritant receptors' is still used, although it has been challenged by several authors (Pack, 1981; Sant'Ambrogio, 1982; Colerige and Coleridge, 1986), and the original term of 'rapidly adapting receptors' is now widely used. Because RARs respond to physiological, as well as pathological stimuli; because their response to irritant stimuli is not well marked in all species; because identification of RARs is based on their adaptation rate; and because the term 'rapidly adapting receptors' implies nothing about the receptor function, which is still uncertain, the term 'rapidly adapting receptors' seems more appropriate than any other at present. I will therefore use it throughout this dissertation.

DISTRIBUTION OF RARs WITHIN THE AIRWAYS

RARs are present in the trachea, the major airways and the intrapulmonary airways (Mortola et al, 1975; and Sant'Ambrogio, 1982). So far information regarding the distribution of RARs is mainly from physiological studies, as the present techniques used in morphological studies do not necessarily distinguish RARs from PSRs, since both these receptors are supplied by myelinated fibers. There-

fore, with the combination of the results from the two methods, one can get a relatively clear picture of the distribution.

In an early study in cats Widdicombe, (1954 b) examined the distribution of RARs in the extrapulmonary airways, and found 14% of RARs in the upper half of the trachea and 46% in the lower half, 26% at the carina, and the remainder distributed in decreasing numbers along the first and second order bronchi. In dogs Mortola et al, (1975) described the distribution of RARs throughout the airways, and found 33% in extrapulmonary airways, most between carina and lung hilum, and 67% in intrapulmonary airways, although only about 5% were in bronchi with diameters smaller than 1 mm. In this study the number of the RARs was found to increase from upper trachea to the lobar bronchi and then to decrease sharply down to the smaller airways.

The estimated concentrations of these receptors in the upper two thirds of the trachea, lower third of the trachea and main stem bronchus were 0.76 receptors/cm^2, 2.76 receptors/cm^2 and 8.08 receptors/cm^2 respectively (Mortola et al, 1975). In addition, direct probing of the mucosa indicated that the receptive field of an individual receptor in the extrapulmonary airway was about 0.8 cm^2 (Sant'Ambrogio et al, 1978). From these figures we can

see that the receptive fields are extensive, that they overlap, and that the overlap is most marked in the main stem bronchi.

Sant'Ambrogio et al (1978) described RARs as being distributed evenly around the circumference of the main stem bronchi and most were supplied by the ipsilateral vagus. In the trachea, most RARs were distributed throughout the ipsilateral hemicircumference, and only about 17% were in the contralateral hemicircumference. In the same study, Sant' Ambrogio et al also described that mucosal resection abolished the response of most RARs to local probing, leaving the response to inflation and deflation intact. This suggests that the part of the sensory arborisation responsible for light touch lies both in or just below the epithelium, while the part responsible for gross mechanical deformation lies in the deeper structures of the airway, possibly the smooth muscle. This finding agrees well with the histological study of Elftman (1943) in which she described myelinated fibers with endings in the bronchial walls, both in the epithelium and in the underlying smooth muscle, and found that the terminal arborisations often ramified in the tracheobronchial wall over a large area of submucosa. It is noteworthy that these end-formations were found to be concentrated at the region of the carina.

RESPONSE TO MECHANICAL CHANGES

The general impression has been that RARs are virtually inactive in eupnea (Knowlton and Larrabee, 1946; Armstrong and Luck, 1974). In guinea pigs (Bergren and Sampson, 1982) and dogs (Sampson and Vidruk, 1975) with lungs ventilated at normal resting rates and tidal volumes, average activities were found to be about 0.3 impulses/sec. In cats, under similar experimental conditions, 41% of RARs were found to be inactive and the overall average activity was about 1 impulse/sec (Armstrong and Luck, 1974). In spontaneously breathing rabbits (with right vagus nerve cut) the average activity was found to be about 0.8 impulses/sec (Mills et al, 1969).

Those RARs that are active under control conditions display a variety of patterns of activity, ranging from a discharge with an expiratory modulation (Luck, 1970), to one with a mainly inspiratory modulation (Sampson and Vidruk, 1975), and to one with no apparent respiratory modulation at all (Mills et al, 1969). The irregular and variable activity of RARs could be partly explained by their multibranching endings, and, in the case of some RARs, by adventitious stimulation from nearby cardiovascular structures (Coleridge and Coleridge, 1986).

The scanty background activity, together with the relatively irregular firing pattern of RARs led investigators to conclude that RARs are unlikely to exert an appreciable influence on the pattern of respiration in eupneic conditions.

The response of RARs to increasing lung volume has been examined by Pack and DeLaney (1983). When the lungs were inflated to a large volume (750 ml) at a constant rate, RAR activity increased progressively as lung volume increased. This response was independent of receptor threshold. Receptor threshold, however, decreased as inflation rate increased. Moreover, because of the dynamic sensitivity of RARs, their activity at any given tidal volume also increased as inflation rate increased. It was concluded that RARs sense the rate of air flow as well as inflation volume (Pack and DeLaney, 1983). Probably because of this, RARs in rabbits fire more actively after vagotomy, and during the hyperpnoea induced by asphyxia (Sellick and Widdicome, 1969). However, inflation volume and airflow are related directly to transpulmonary pressure and the rate of change of transpulmonary pressure (dp/dt). In addition, RARs adapt more rapidly when the lungs are inflated at constant volume than when they are inflated at constant pressure (Widdicombe, 1954 b). This suggests that transpulmonary pressure is a better indication of the stimulus to RARs

than lung volume. So it is reasonable to assume that RARs actually respond to changes in tension in the airway wall in which they lie, and these changes are correlated most closely with transpulmonary pressure and dp/dt. Widdicombe and his coworkers described the response of intrapulmonary RARs in pathological conditions of the lung, such as pneumothorax, pulmonary congestion and embolism, and discussed the possible reasons for the increased discharge in those situations. They attributed the increase mainly to the increased pull of a stiffened lung parenchyma on the airway walls (Mills et al, 1969; Widdicombe, 1974) as did Armstrong and Luck (1976) in a study of pulmonary embolism in cats. However, all the above investigators stressed that chemical effects on the nerve endings could not be excluded.

Sellick and Widdicombe (1970) also reported that RAR activity was inversely correlated with lung compliance, in the sense that after forced deflation, dynamic lung compliance decreased and the spontanous discharge of the receptors increased, and after hyperinflation compliance increased and the spontanous discharge decreased. However they discounted the possibility that RAR activity was proportionately related to graded changes in lung compliance. Moreover, it is difficult to determine in Sellick and Widdicombe's experiments whether the increased activity was actually due to decreased lung compliance or to increased

transpulmonary pressure. When compliance decreases the swing of transpulmonary pressure increases, and I think that it is important to attempt to distinguish the effects of these two factors.

RESPONSE TO CHEMICALS

RARs have been reported to respond to a variety of chemicals, such as ammonia vapor, ether, cigarette smoke, histamine, prostaglandins (PGs) and serotonin. However, there is a species difference in regard to the chemical response of RARs. For example, inhalation of ammonia vapor increases RAR activity in cats (Armstrong and Luck, 1974), guinea pigs (Bergren and Sampson, 1982) and rabbits (Mills et al, 1969) but appears to have little effect in dogs (Sampson and Vidruk, 1975). Similarly, cigarette smoke stimulates RARs in rabbits (Sellick and Widdicombe, 1971) and guinea pigs (Bergren and Sampson, 1982) but not in dogs (Sampson and Vidruk, 1975). The difference between species suggests that the response of RARs to irritant vapors is not universal, and it gives us a clue that chemical sensitivity is unlikely to be a primary function of RARs.

The response of RARs to histamine has attracted most attention, because histamine is known to be released in the airways in asthma and pulmonary anaphylaxis. Histamine

is released from mast cells in the lungs, as a consequence of IgE mediated antigen antibody reactions (Chiesa et al, 1975). Other chemicals known to stimulate RARs, such as PGF2α can be released by a number of factors such as anaphylaxis, hyperventilation and mechanical stimulation of the lungs (Said, 1973). Both histamine and PGF2α cause bronchoconstriction, and make the lungs stiffer. Hence in many situations, chemical and mechanical effects may coexist. That is, mechanical change can cause chemical release and the chemicals also can induce a mechanical change.

Histamine, either injected intravenously or given as an aerosol, stimulates RARs in rabbits (Mills et al, 1969), guinea pigs (Bergren and Sampson, 1982), cats (Armstrong and Luck, 1974) and dogs (Sampson and Vidruk, 1975; Vidruk et al, 1977; Coleridge et al, 1978). The degree of stimulation is less, however, and in some cases stimulation is abolished completely, if the bronchoconstrictor effect of histamine is partly or completely prevented by administration of a ß adrenergic agent (Mills et al, 1969; Sampson and Vidruk, 1978). However, in dogs Sampson and Vidruk (1978) observed that isoproterenol did not abolish the RAR response to histamine completely, although isoproterenol did reduce the tracheal pressure swings produced by histamine. They also observed that topical application of histamine can stimulate RARs without a gross change in lung mechanics.

Furthermore, they observed that RAR activity increased much more in response to local application of an aerosol of histamine than to local application of an aerosol of acetylcholine (Ach) even though both applications produced changes in transpulmonary pressure of similar magnitude. Thus, they concluded that the direct chemical effect of histamine on the receptor endings is probably more important than its secondary mechanical effects. Nevertheless it seems likely that RAR sensitivity to histamine in dogs is a matter of sensitization rather than stimulation outright, because RAR activity induced by histamine usually ceases when the artificial ventilator is switched off and resumes when the ventilator is swiched on again. This suggests that the background mechanical stimulation is essential to the response (Coleridge et al, 1978). It is noteworthy that in dogs PGE2, a powerful bronchodilator which is also irritant to the airways, does not stimulate RARs (Coleridge et al, 1978). Once again this suggests that an increase in lung stiffness is very important in stimulating RARs.

REFLEX EFFECTS OF RARs

A major difficulty in establishing the reflex effects of RARs is that there is no reliable method of selectively altering their activity. Most procedures that stimulate RARs also change the activity of other pulmonary receptors.

However, the excitatory influence of RARs on inspiratory motor output seems clear from all studies published so far.

Larrabee and Knowlton (1946) presented evidence that stimulation of RARs by a large rapid lung inflation causes an abrupt increase in phrenic nerve discharge, instead of the inhibition of phrenic discharge observed when the lungs are inflated more slowly. They suggested that input from RARs is excitatory to the respiratory center, in contrast to input from PSRs, which was thought to be purely inhibitory. They also suggested that RARs are the receptors responsible for spontaneous deep breaths or sighs, which sometimes occur when deep breathing is evoked by other mechanisms. For example, they observed that sporadic deep breaths are evoked during CO_2 rebreathing and only occur when the vagus nerves are intact. Widdicombe (1954 c) confirmed these observations, and found that the excitatory effects on phrenic activity were not blocked by vagal cooling until the temperature was 2-3°C lower than that required to block the inhibitory inflation reflex (Hering-Breuer reflex).

Davies and Roumy (1982) applied both positive and negative pressure pulses of 100 ms duration to the tracheal cannula of rabbits during inspiration and expiration, respectively, after blocking PSRs by high concentrations of

SO_2. They found that either a positive pressure pulse or a negative pressure pulse produced an augmented breath, and after an augmented breath it was impossible to produce another one for at least 1 minute. This further confirms the theory that RARs have excitatory effects on inspiratory output.

Pack et al (1981) also observed in dogs an augmentation of phrenic neural activity evoked by increased rates of lung inflation. This augmentation consisted of an increase in the slope of the integrated phrenic neurogram, and was noted even with a normal tidal volume. This fits in well with the observation that RARs are sensitive to the rate of inflation (Pack and DeLaney, 1983). Moreover, in the same study, Pack et al (1981) also observed that if inflation rate was increased to a critical level, an augmented breath was produced. This was followed by a refractory period in the phrenic neural response, which has been described by others after augmented breaths (Reynolds, 1962; Davies and Roumy, 1982).

The above evidence leads us to conclude that RARs cause excitation of inspiratory output, i.e. deep breaths, rather than shallow ones. Hence it seems unlikely that RARs are responsible for the rapid shallow breathing caused by many chemical irritants, and it seems more likely that

the latter pattern of breathing is the result of C-fiber stimulation (Coleridge et al, 1983).

It has also been suggested that RAR input shortens expiratory time (Te). Fishman et al (1973), using differential blockade of the vagus nerves by cooling in conscious dogs, observed that after the Hering-Breuer reflex was abolished, further cooling of the vagus nerves could increase Te. They suggested, therefore, that these residual effects on Te were due to RARs. Davies et al (1978) reached the same conclusion. They used SO_2 to selectively block PSRs in rabbits, and when they subsequently cut the vagus nerves bilaterally they observed a lengthening of Te. However, these approaches do not provide direct evidence to support the hypothesis that RARs shorten Te, because blockade of input from C-fibers may have been partly responsible for the effects observed (Coleridge and Coleridge, 1984; Pisarri et al, 1986). Better evidence for the shortening effect of RARs on Te was obtained by Davies and Roumy (1982), who found that Te often decreased in the two or three breaths after an augmented breath. RARs were also thought to have an indirect effect on the duration of inspiration (Davies and Roumy, 1986). Nevertheless, I think that further study of the possible effects of RAR input on Te would be appropriate.

The hypothesis that RARs cause bronchoconstriction was based on the observation that in several conditions, for example, pneumothorax, pulmonary congestion, microemblism and histamine injection, the increased RAR activity was often accompanied by bronchoconstriction (Mills et al, 1969; Sillick and Widdicombe, 1969). However, it also has been reported that in these conditions C-fibers are also stimulated (Armstrong and Luck, 1976; Paintal, 1973). In addition, C-fibers participate in many pathological processes and also cause bronchoconstriction (Roberts et al, 1981; Coleridge and Coleridge, 1984). Actually there is no direct evidence to support the idea that RARs evoke a vagally mediated bronchoconstriction, and it may be dangerous to come to such a conclusion by simply relying on a correlation, as pointed out by Coleridge and Coleridge (1986). However, we cannot exclude the possibility that RARs do produce bronchoconstriction either, and if we could devise some means of stimulating them selectively, it should be easy to investigate the possibility.

SECRETION FROM AIRWAY SUBMUCOSAL GLANDS

Although RARs are thought to cause airway secretion (Widdicombe, 1986), this has not been clearly established. If RARs have a major role in defence reflexes of lung origin, it seems important to investigate this aspect of their

reflex properties.

The airways are innervated by sympathetic, parasympathetic and nonadrenergic noncholinergic nervous systems, regulating the smooth muscle tone and submucosal gland secretion (Nadel, 1983; Nadel and Barnes, 1984; Nadel et al, 1986). The airway receives ten times more cholinergic nerve endings than adrenergic endings (Murlas et al, 1980). Stimulation of vagus nerves increased submucosal gland secretion, which was blocked by atropine (Ueki et al, 1980). Ach seems to be the most important mediator involved in the reflex secretion of the glands. Many reflexes are known to stimulate gland secretion via the vagal nervous pathways, such as mechanical irritation of the laryngeal epithelium (German et al, 1980), gastric irritation (German et al, 1982), carotid chemoreflex (Davis et al, 1982 a) and the reflexes induced by stimulating pulmonary (Schultz et al, 1985) and bronchial C-fibers (Davis et al, 1982 b).

PRESENT RESEARCH

The present investigation began with observations made in experiments in dogs with open chest and lungs ventilated at a constant tidal volume and frequency, in which my colleagues and I were examining the effects of vagal cooling on conduction in the various types of pulmonary

afferents. We found that after RARs were identified by hyperinflating the lung their scanty and irregular discharge often disappeared completely, making it impossible to examine the effects of cooling on many of them. We found, however, that if positive end-expiratory pressure (PEEP) was removed from the ventilator outlet for five or six ventilator cycles and then replaced, activity in the RAR was often restored. The restoration of RAR discharge coincided with a small decrease in lung compliance (Pisarri et al, 1986). I reasoned, therefore, that the low control activity of RARs reported in previous studies was the activity observed at high lung compliance, i.e. after the lungs had been hyperinflated to identify the endings, and that during quiet breathing, when lung compliance may fall to 20-30% below maximum (Ferris and Pollard, 1960), the receptors might become much more active. I also felt that RARs might provide an important signal related to small, physiologic changes in compliance.

I therefore undertook the systematic study described in this dissertation, and examined the effects of small, sequential changes in lung compliance on RARs in rabbits and cats, since these are the species in which the characteristics of RARs have been described most frequently. The animals were ventilated at constant tidal volume and frequency, the chest was opened widely, maximal compliance was obtained by hyperinflating the lungs, and then compliance was reduced

in steps by removing PEEP for short periods and finally by applying a small negative end-expiratory pressure for 2-4 cycles. C_{DYN} was then restored to control by hyperinflating the lung. I attempted to examine the following issues:

1. Whether small changes of dynamic lung compliance (C_{DYN}) in the physiological range cause proportional changes in RAR activity and if so which variable, (lung compliance, tracheal pressure or rate of change in tracheal pressure and airflow rate) is the major determinant of RAR activity. In order to identify the major determinant, the response of RARs to decreasing C_{DYN} was compared with the response to increasing the tidal inflow without changing the duration of the ventilator cycle. Responses were compared for similar increases in transpulmonary pressure and rate of change of pressure. Atropine was used to determine whether reflex change in bronchomotor tone and hence in the flow resistive component of C_{DYN}, contributed to the RAR response to decreased C_{DYN}.

2. To what extent the increase in RAR activity after right atrial injection of histamine is due to the indirect mechanical stimulation from a decrease in lung compliance.

3. Whether PSRs respond to changes in C_{DYN} in the same manner as RARs.

4. Whether there is any evidence that the basal activity of RARs affects breathing during differential cooling of the cervical vagus nerves.

5. Whether stimulation of RARs will reflexly increase secretion by airway submucosal glands in dogs. To study this, secretion rate was measured during mechanical stimulation of RARs before and after RAR input was blocked by vagal cooling or vagotomy.

METHODS

GENERAL

ANESTHESIA

Experiments were conducted on adult rabbits, cats and dogs of both sexes. Rabbits (3.5 - 5.2 kg) were anesthetized with 20% urethane (1 g/kg) injected slowly into an ear vein. Supplemental doses (about one eighth of the initial dose) were given through a femoral venous catheter when necessary to maintain surgical anesthesia. Cats (2.6 - 5.5 kg) were anesthetized with sodium pentobarbital (Nembutal; 30 to 35 mg/kg) injected slowly into a foreleg vein; supplemental dose was given by intravenous drip of 0.1% sodium pentobarbital in 0.9% saline at the rate of about 4 mg/kg/hour throughout the experiments to maintain anesthesia. Dogs (16.3 - 26.3 kg) were anesthetized with α-chloralose (80 mg/kg i.v.). Supplemental doses (10 mg/kg i.v.) were given hourly to maintain anesthesia. The depth of anesthesia was checked by testing the corneal and withdrawal reflexes. Flaxedil (1 mg/Kg) was administered intravenously in some experiments to abolish spontaneous respiratory movements. Periodically, the effect of flaxedil was allowed to wear

off so that the depth of anesthesia could be assessed and adjusted.

GENERAL PROCEDURES

The neck was incised in the midline. The trachea was exposed and a tracheal cannula was inserted as low in the neck as possible. The right or left carotid sheath containing the vagus nerve was dissected from the connective tissue for recording of afferent impulses. The lungs were ventilated with 50% O_2 in air by Harvard respirators (model 670 for cats and rabbits and model 613 for dogs). Tidal volume (V_T) was set at about 8 to 10 ml/kg body weight in cats and rabbits, and 15 ml/kg body weight in dogs. Tidal CO_2 was monitored by a Beckman LB-1 gas analyzer (see below). Ventilatory frequency (about 15 to 20 cycles/min) in cats and rabbits, and about 10 to 15 cycles/min in dogs) was adjusted to maintain end-tidal CO_2 at about 30-35 mmHg. A positive end-expiratory pressure (PEEP) was maintained by placing the expiratory outlet tube of the respirator under 3-4 cm of water to prevent the lung from collapsing at the end of deflation. Arterial blood samples were taken periodically from a femoral artery and their pH, PCO_2, PO_2 and HCO_3^- were measured by a Corning blood gas/pH analyzer (Model 175). Any metabolic acidosis was corrected by administration of 2.8% $NaHCO_3$ solution intravenously.

Rectal temperature was recorded with a probe (401) connected to a YSI (Model 43TA) tele-thermometer, and was maintained at about 38°C by placing the animal on a thermal water pad (Model K 20, Hamilton Industries Inc.), and also by covering the animal with a blanket when necessary.

SURGERY

The chest was opened in the midline, and large vessels were ligated carefully. Bleeding was controlled by cautery in dogs and cats, or by ligating small vessels in rabbits. Special care was taken not to cut the internal mammary vessels during thoracotomy. Bone wax was employed to stop bleeding along the cut edges of the sternum. The parietal pleura was opened and the chest walls were retracted, so that chest was kept widely open throughout the experiments. The opened chest was covered by a plastic sheet to prevent evaporation.

RECORDED VARIABLES

Arterial blood pressure was measured by a Statham strain gauge transducer (P23Gb) connected to a catheter placed in the descending aorta via the right femoral artery. Heart rate was measured by a cardiotachometer (Grass 7P4)

triggered by the pulsatile blood pressure or by an electrocardiogram lead II. Tracheal pressure was measured from a sidearm of the tracheal cannula by a Statham strain gauge transducer (P23Gb). Tracheal CO_2 was monitored by a Beckman LB-1 gas analyzer, gas samples being drawn through a microcatheter from a sidearm of the tracheal cannula to the pickup unit of the gas analyzer. Pressure in the pickup unit was reduced to about 1/2 atmosphere so that a rapid and accurate analysis of tracheal CO_2 could be obtained from a small gas sample. Impulse frequency of vagal afferents was counted by a ratemeter (see NERVE RECORDING). In some cases vagal temperature was monitored by thermistor (see Vagal Cooling Procedure).

All the variables described above were recorded continously by a Grass Polygragh. Vagal action potentials (see NERVE RECORDING), together with tracheal pressure and blood pressure, were also recorded by a Gould Electrostatic Recorder (ES 1000).

ANALYSIS OF DATA

Data for groups are reported as mean ± SE. Student's paired t test and nonparametric Wilcoxon paired (sign rank) test were used to compare differences between two groups of data. Differences were considered statistically signifi-

cant at $P<0.05$.

AFFERENT STUDIES

Since the cat and the rabbit have been the species most frequently used to examine the afferent and reflex properties of rapidly adapting receptors (Coleridge and Coleridge, 1986), the afferent studies were conducted mainly in these two species; however, a few afferent studies were carried out in dogs. The effects of lung deflation and decreased dynamic lung compliance (C_{DYN}) on pulmonary rapidly adapting receptors (RARs), slowly adapting pulmonary stretch receptors (PSRs) and pulmonary C-fibers were studied; the contribution of decreases in C_{DYN} to the stimulating effects of histamine on RARs were also examined. The detailed techniques and experimental procedures will be described in the following sections.

NERVE RECORDING

With the aid of a dissecting microscope, the vagus nerve (either right or left) was separated from the carotid sheath with watchmaker's forceps and fine scissors, and was placed upon a small, black dissecting platform (1 cm wide for cats and rabbits, 1.5 cm wide for dogs). The vagal sheath was carefully opened with a pair of fine scissors

and was removed from that part of the vagus nerve lying on the platform. In dogs it is particularly important to remove all the sheath on the platform, because the vagal sheath in this species contains many blood vessels, and even a small amount of blood collecting on the platform would interfere with the nerve recording. The nerve was then covered by a pool of warm (37°C) mineral oil. A small afferent bundle was cut from the vagus nerve and placed upon the recording electrodes (see below), the main trunk of the vagus nerve being left intact. The nerve bundle was then divided and subdivided into finer and finer strands until action potentials of an uniform amplitude were obtained, that is, a physiological 'single fiber' was obtained.

A pair of bipolar silver recording electrodes was brought into place above the nerve. One electrode was grounded to the main nerve trunk by a thin cotton thread soaked in 0.9% NaCl solution; the nerve filament was looped over the other electrode. The electrodes were connected to a High Impedance Probe (Model HIP 511) from which the output was led to a Grass (P 511) amplifier. After suitable amplification, action potentials from single fiber strands of the vagus nerve were displayed on an oscilloscope (5A18N, Tektronix Inc.), and were also monitored by a loudspeaker. In addition, a voltage analogue of impulse frequency was produced by a ratemeter (Frederick Haer and Co.) at a bin

width of 0.1 sec. In some experiments impulses per ventilatory cycle were counted by a Winston rate meter, the counts being reset at the end of each ventilatory cycle by a switch triggered by the respirator.

When impulses were recorded from two fibers in the same vagal strand, an amplitude analyzer, whose window discriminator was set to accept potentials of a particular amplitude, generated a voltage pulse for each impulse which appeared in the window. The signal was then led through a rate interval analyzer, which counted the number of pulses per unit time. A second rate interval analyzer counted the action potentials that appeared above the upper limit of the ratemeter window. Thus the impulse activity in two afferent fibers could be analyzed simultaneously, provided the potentials were of different amplitude.

IDENTIFICATION OF PULMONARY VAGAL AFFERENTS

Identification of pulmonary vagal afferents is based on their afferent properties. Although larger fibers often have larger action potentials, action potential amplitude also depends on other conditions, such as the contact between the afferent fiber and the electrodes, and the number of vagal fibers contained in the tested filament. Therefore, the claim made by Mills et al (1969) that RARs and PSRs

could be distinguished by the amplitude of their action potentials is not valid (see Fig. 2-1). Thus, the amplitude of action potential will not be considered in identifying vagal afferents.

Identification of RARs

RARs were first identified by their rate of adaptation. The adaptation index, first defined by Knowlton and Larrabee (1946) and then elaborated by Widdicombe (1954 b) (see INTRODUCTION), was calculated by the following formula and expressed as a percentage.

$$\text{Adaptation index} = \frac{\text{peak f} - \text{average f during 2nd sec of inflation}}{\text{peak f}} \times 100\%$$

When stimulated by a constant pressure inflation of 20 cm H_2O, receptors with adaptation indices above 70% were considered to be RARs. A few receptors with an adaptation index between 70% and 55% were also taken to be RARs if they possessed other characteristics of RARs. During constant pressure inflation, RAR activity either adapts completely or persists at low frequency with irregular interspike intervals (Fig. 2-2). RARs were also identified by inflating the lungs with 3 or 4 tidal volumes (V_T). RARs fired more

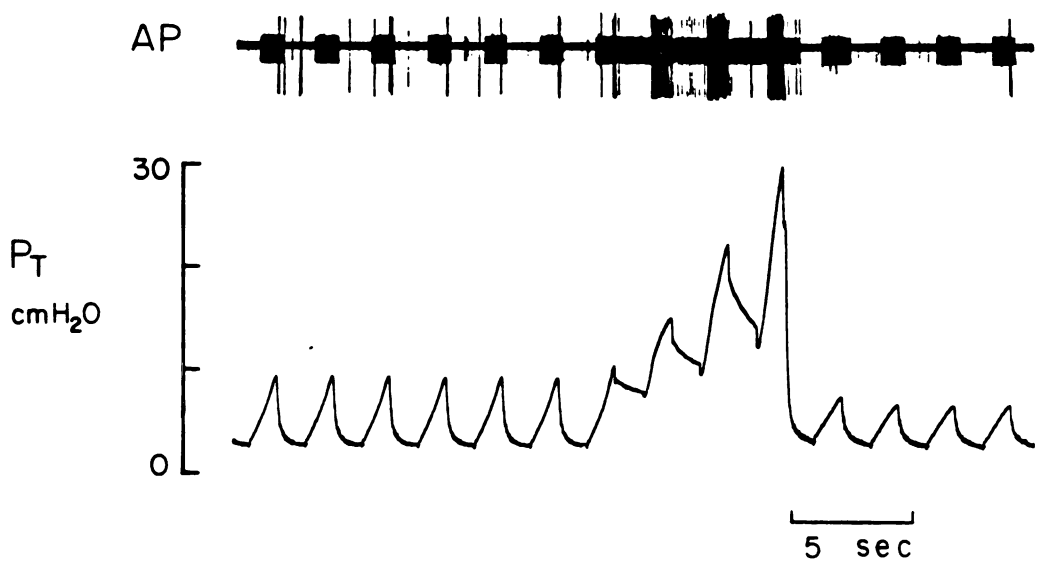

Fig. 2-1. The responses of a rapidly adapting receptor (large spikes) and slowly adapting receptor (small spikes) to hyperinflation of the lungs. AP, action potentials; P_T, tracheal pressure. Note that the rapidly adapting receptor responded to inflation intermittently with a burst at each peak of inflation wheras the slowly adapting receptor responded to inflation with a continuous discharge.

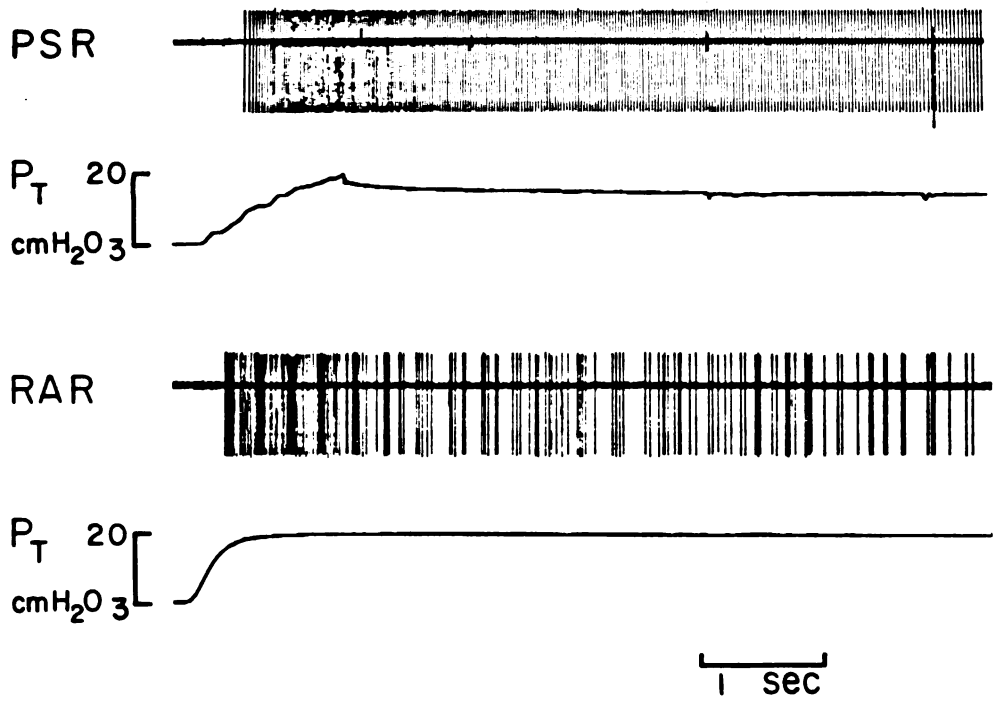

Fig. 2-2. Effect of constant pressure inflation of the lungs on a slowly adapting pulmonary stretch receptor (PSR) and a rapidly adapting receptor (RAR). P_T, tracheal pressure. Note that during maintained inflation the PSR adapts slowly with a regular interspike interval, and the RAR adapts rapidly with an irregular interspike interval.

and more at the successive peaks of inflation but they ceased firing between inflations (Fig. 2-1). This method was found to be a reliable and convenient way to identify RARs. RARs were also identified by their firing pattern, which characteristically is sparse and irregular during control ventilation (Fig. 2-3), and often has a cardiac rhythm during deflation (Knowlton and Larrabee, 1946). Above all, RARs are characterized by the irregularity of their interspike intervals.

The location of the RARs was determined by gently probing the lung with a fine glass rod to find the sensitive point from which bursts of impulses were most easily elicited.

Identification of PSRs

PSRs were identified by their characteristic respiratory modulation, by their regular discharge and interspike intervals during control ventilation (Fig. 2-3), and by their slowly adapting response to maintained inflation (Fig. 2-2). Hyperinflation of the lungs (3 or 4 V_T) was an effective way to demonstrate the slow adaptation of these receptors (Fig. 2-1).

Identification of C-fibers

Pulmonary C-fibers were identified by their sparse and irregular discharge, by their short latency (1 to 3

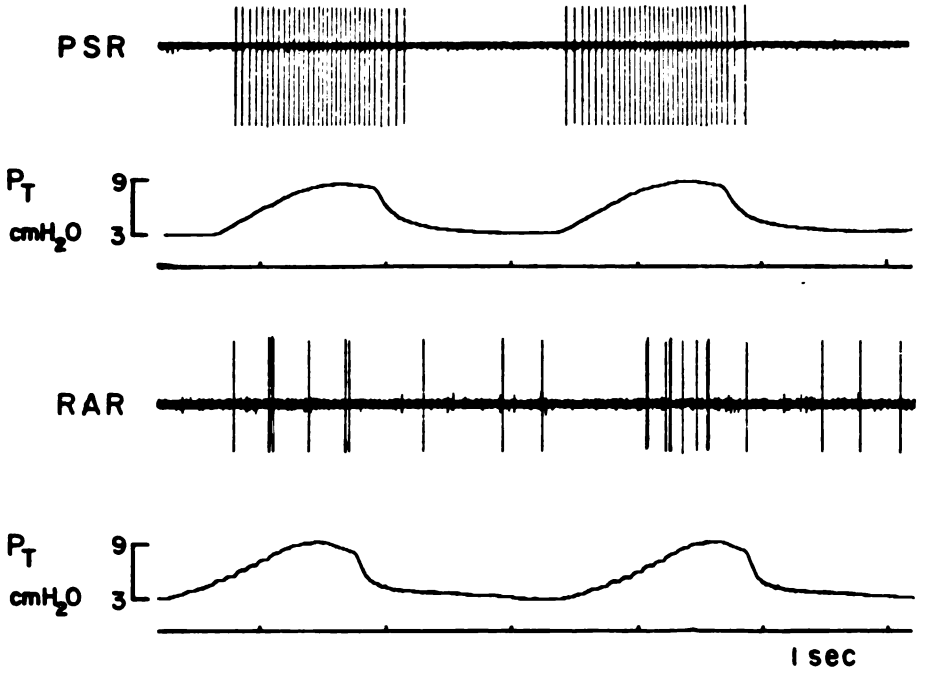

Fig. 2-3. Discharge patterns of a slowly adapting pulmonary stretch receptor (PSR) and a rapidly adapting receptor (RAR) in a cat. P_T, tracheal pressure. Note that PSR activity has a clear respiratory modulation and a regular interspike interval. In contrast, though RAR activity increases during inflation, the respiratory modulation is less obvious and the activity also occurs during deflation; the interspike interval is irregular and unpredictable.

sec) response to right atrial injection of capsacin (see below) and by their response to hyperinflation (2 or 3 V_T) of the lungs (Coleridge and Coleridge, 1977). In some cases C fibers were also identified by their conduction velocities (0.5 to 2.4 m/sec), which were measured by stimulating the cervical vagus trunk as low in the neck as possible at two positions, 1 cm apart, using two pairs of electrodes fixed in a shielded assembly. Conduction velocities were derived from the conduction time between the stimulating electrodes. Pulmonary C-fibers were also located by probing the lungs with a fine rod, as in the case of RARs.

Injection of capsaicin. A stock solution was prepared containing 10 mg capsaicin (Sigma Chemical Co.), 0.1 ml 96% ethyl alcohol and 1 drop of 'Tween 80' (Atlas Manufacturing Co. Ltd.) made up to 10 ml with saline (NaCl solution 0.9 g/100 ml) (Coleridge et al, 1964). This was diluted as required with 0.9% saline to give a dose of 10-20 µg capsaicin/kg body weight in 0.2 ml saline. The solution was kept at 40°C until use. Capsaicin was flushed into the circulation with 0.5 ml of 0.9% saline solution. The injection was usually completed within 1-2 sec.

MEASUREMENT OF DYNAMIC LUNG COMPLIANCE

Lung compliance is defined as the volume change per

unit pressure change across the lungs. In the present experiments open chest animals were used, and the lungs were ventilated artificially from a positive end expiratory pressure with a fixed V_T and cycle length. Thus, dynamic lung compliance was calculated from $\Delta V/\Delta P$. Here ΔV is tidal volume and ΔP is the change of tracheal pressure during each ventilatory cycle. That is to say, C_{DYN} was calculated from the tidal volume of the ventilator divided by the difference between the tracheal pressure at the peak of inflation and that at the end of deflation (i.e. PEEP).

PROTOCOL

Studies on RARs

Effect of decreasing C_{DYN}. Observations were made with the lungs ventilated at constant tidal volume and frequency. At the beginning of each set of observations, C_{DYN} was increased to a maximum. The expiratory line between tracheal cannula and respirator was occluded briefly to expand the lungs progressively for 3 or 4 ventilator cycles, peak tracheal pressure increasing to about 25 cm H_2O (Fig. 2-4 A). After release of the expiratory line, tracheal pressure at the peak of normal inflation was usually less than that before the hyperinflation, and lung compliance was assumed to be maximal because no further decrease in tracheal pressure occurred when hyperinflation was repeated.

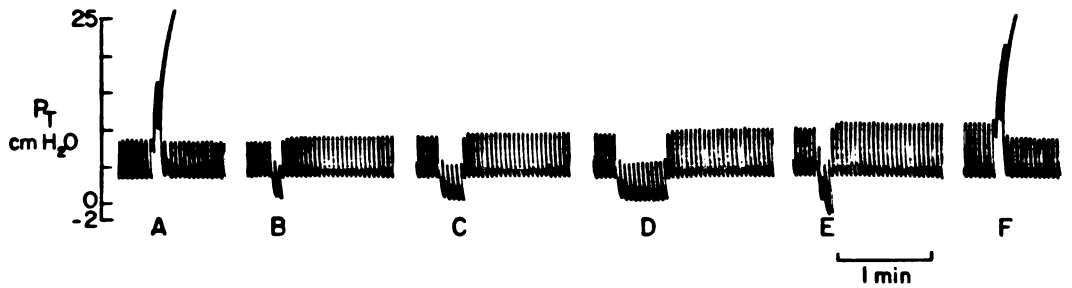

Fig. 2-4. Record of tracheal pressure (P_T) in a rabbit, showing the sequence of procedures for changing C_{DYN}. The lungs were ventilated at constant tidal volume and frequency throughout, apart from brief periods of hyperinflation in A and F. A, lungs hyperinflated initially to obtain maximal compliance. B, C and D, PEEP removed for 2, 5 and 10 ventilator cycles, respectively, by opening the expiratory line to atmosphere. E, expiratory line connected for 2 ventilator cycles to a reservoir in which pressure held at -2 cm H_2O. Note that after each restoration of PEEP, P_T at the peak of inflation increased, indicating a reduction in C_{DYN}. F, the lungs were finally hyperinflated to restore C_{DYN} to control.

After maximal C_{DYN} had been established, control receptor activity was recorded for 1-2 minutes. Compliance was then reduced to 50-60% of maximum in 4 steps: 3 of the 4 step reductions in C_{DYN} were made by opening a sidearm on the expiratory outlet of the respirator to remove PEEP for 2, 5, and 10 ventilator cycles (Fig. 2-4 B, C, D); the fourth reduction was made by connecting the expiratory outlet for 2 or 3 cycles to a reservoir in which the pressure was held at -2 cm H_2O (Fig. 2-4 E). After each of the 4 maneuvers, PEEP was restored by closing the sidearm on the expiratory outlet, so that C_{DYN} decreased. Receptor activity was then recorded for 100-120 sec, impulse frequency being averaged over successive periods of approximately 20 sec (5 to 7 complete ventilatory cycles). After each sequence of observations, the lungs were hyperinflated (Fig. 2-4 F) to restore C_{DYN} to the control level (Fig. 2-4 A).

Effect of atropine. C_{DYN} calculated in the present experiments also includes a component related to airway resistance, which may vary with changes in vagal efferent discharge to airway smooth muscle. To examine possible effects of vagal efferent discharge, RAR activities at different levels of C_{DYN} were compared before and after administering atropine (1 mg/kg i.v.).

Effect of C_{DYN} on response to static lung inflation. The effect of C_{DYN} on the RAR response to static lung inflation was also examined. The lungs were inflated abruptly to about 10 or 20 cm H_2O for 10 to 20 sec by clamping the expiratory tube and connecting the inspiratory tube to a constant pressure reservoir. The effects of static inflation were examined at two levels of C_{DYN}: when C_{DYN} was maximal and when it had been reduced by 30-50%.

Comparison of the effects of increasing lung stiffness with those of increasing tidal volume. Tidal airflow was increased in steps by increasing tidal volume without changing the duration of inflation or total cycle length, PEEP being held constant. The stepwise increases in peak tracheal pressure produced in this way were comparable to those produced by the stepwise decreases in C_{DYN} (i.e. increases in lung stiffness), as described above. Each step increase in tidal volume was maintained for about 30 sec. Receptor activity was averaged over 5 to 7 cycles (approximately 20 sec) at each step, and was compared with that induced by reducing C_{DYN}. Linear regression lines of receptor activity against tracheal pressure were constructed for the changes in lung stiffness and the changes in tidal volume.

Effect of histamine. Experiments were performed to

determine to what extent the response of RARs to histamine could be ascribed to the decrease in C_{DYN} (increase in lung stiffness). The RAR response to a bolus injection of histamine acid phosphate (50 µg/kg in 0.9% saline of 0.2 ml) was compared with that to an equivalent increase in lung stiffness. RAR activity after histamine was calculated by counting impulses over 3 consecutive ventilatory cycles and expressed as impulses/sec.

RAR activity was first recorded at different levels of lung stiffness (see above) and a linear regression line was constructed. After histamine was injected, RAR activity was sampled at the maximal increase in lung stiffness and at the maximal activity of RARs. Fig. 2-5 illustrates the procedure. The interval between these two events was noted and the activities were compared. The activities were also compared with the RAR activity calculated from the linear regression line.

Studies on PSRs

Effect of decreasing C_{DYN}. PSRs were divided into two groups, low threshold and high threshold, according to their firing pattern. The low threshold PSRs are active at end-expiratory volume, whereas the high threshold PSRs are silent at end-expiratory volume and begin to fire only during inflation (Paintal, 1966; Sant'Ambrogio, 1982). The

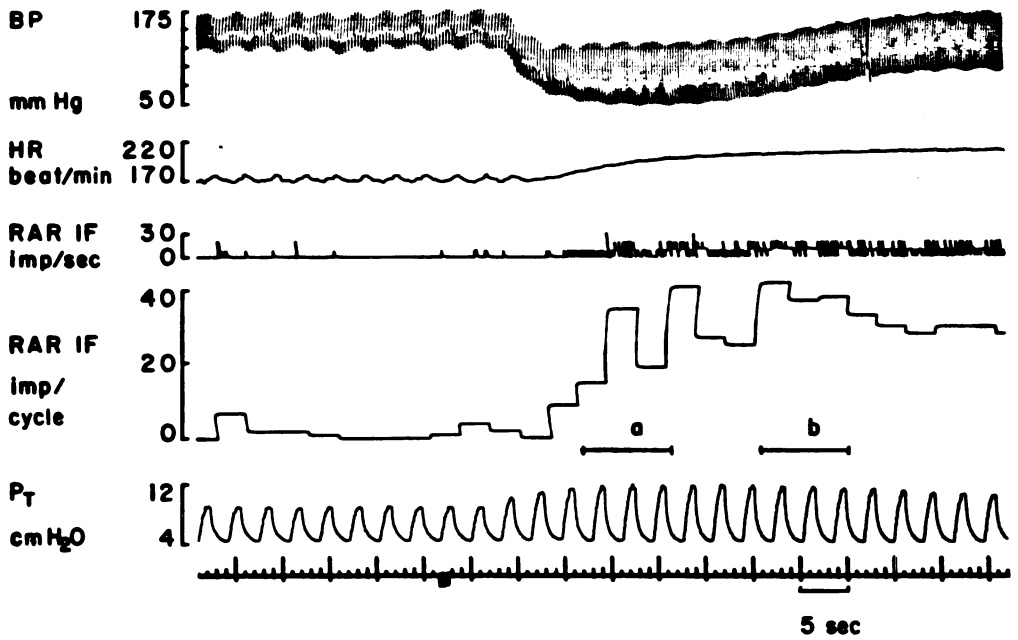

Fig. 2-5. Stimulation of a rapidly adapting receptor (RAR) by right atrial injection of histamine (50 µg/kg, at signal mark) in a cat. BP, blood pressure; HR, heart rate; RAR IF, RAR impulse frequency; P_T, tracheal pressure. RAR activity at peak lung stiffness was sampled during the period denoted by 'a' (3 consecutive ventilator cycles). Maximal RAR activity was sampled during the period denoted by 'b' (3 consecutive ventilator cycles).

two groups of PSRs were analyzed in terms of mean activity, peak activity and minimal activity. Mean activity was calculated by averaging PSR activities over 5 to 7 complete cycles (approximately 20 sec). Peak activity was defined as the highest frequency during 0.1 sec in each ventilatory cycle (averaged over five consecutive cycles). Minimal activity in high threshold PSRs was expressed by the duration of the pause during deflation, and minimal activity in low threshold ones was expressed by the average lowest activity in 0.4 sec during deflation (over 5 ventilatory cycles). PSR activities were also compared at different levels of C_{DYN}.

Comparison of increasing lung stiffness with increasing tidal volume. The experimental procedure was the same as that used in the studies on RARs.

Studies on C-fibers

Since C-fibers fired irregularly, their mean activity was calculated by counting impulses over about 2 minutes (20 to 30 complete ventilatory cycles) and was expressed as impulses/sec. C-fiber activities were compared at two different levels of C_{DYN}, at maximal C_{DYN} and at 60% of maximal C_{DYN}.

EFFECT OF VAGAL COOLING ON CONDUCTION IN PULMONARY FIBERS

Vagal Cooling Procedure

Cooling the vagus nerves is the most widely used and the most repeatable method for differential block of afferent vagal fibers; conduction in myelinated fibers is blocked at 6 to 8°C whereas conduction in C-fibers continues down to 0°C (Paintal, 1965; Franz and Iggo, 1968; Coleridge and Coleridge, 1984). In the present studies conduction of impulses in the right and left cervical vagus nerves was blocked as follows. Each vagus nerve was freed for about 3-4 cm from the carotid sheath as low in the neck as possible and was placed in a groove on the platform (2 cm wide) of a stainless steel cooling device through which alcohol of different temperatures was circulated. The sides and bottom of each platform were insulated with a layer of silicone elastomer (Dow). To reduce thermal gradients, the nerve and adjacent surface of the platform were covered with a warm (40°C) solution of 4% agar in 0.9% saline, which upon cooling, gelled to form a semisolid layer 1 cm thick. The temperature of each platform was measured with a thermistor (Yellow Springs Instrument 729) and was recorded by the Grass polygraph. In some experiments a needle thermistor (Yellow Springs Instrument 524) was inserted through the vagal sheath, so that the thermistor tip was between the sheath and the nerve, and the temperature

of the vagus nerve could be measured directly.

Protocol

Conduction of impulses in the cervical vagus trunks in dogs was blocked progressively by slowly cooling the nerves at the rate of approximately -1.5°C/min. Then, the mean activities of vagal afferents were measured at vagal temperatures in the range over which conduction in afferent fibers is known to be blocked. Thus the control values were compared with the values obtained at 10, 7, 5, 3, and -1.5°C. The rate of cooling was sufficiently slow to permit analysis of 5 respiratory cycles at each temperature, and the mean of the 5 cycles was taken; variability was small.

REFLEX STUDIES

EFFECTS OF RARs ON TRACHEAL SUBMUCOSAL GLAND SECRETION

The experiments on secretion were conducted on dogs, because there are few submucosal glands in rabbits (Nadel et al, 1986), and the tracheal submucosal gland secretions in cats are insufficiently viscous for the methods employed here. In dogs tracheal submucosal glands produce viscous secretion, therefore the secretion rate was more easily assessed with the present method of measurement.

Measurements of Secretion

The method used to measure the secretion of tracheal submucosal glands was first developed by Davis and Nadel (1980). A segment of trachea immediately caudal to the larynx, and usually including six cartilaginous rings, was incised ventrally in the midline and transversely across both ends of the midline incision, the transverse incisions being carried round the cartilaginous rings but stopping short of the posterior wall, which was left intact. Each midline cut edge was attached by nylon threads to a light plastic bar and was pulled laterally to expose the mucosal surface (Fig. 2-6).

Previously formed secretions were removed with small squares of absorbent tissue soaked in 0.9% saline. The mucosa was then dried with absorbent tissue and was sprayed with powdered tantalum (an inert metal) until the surface was coated by a thin uniform layer. The tantalum layer prevented the normal ciliary dispersion of secretions from the openings of the submucosal gland ducts, and the accumulated secretions elevated the tantalum layer to form hillocks. Counts of the hillocks appearing in a given area in unit time provided an index of the rate of secretion.

The mucosa covering the tracheal cartilage was viewed

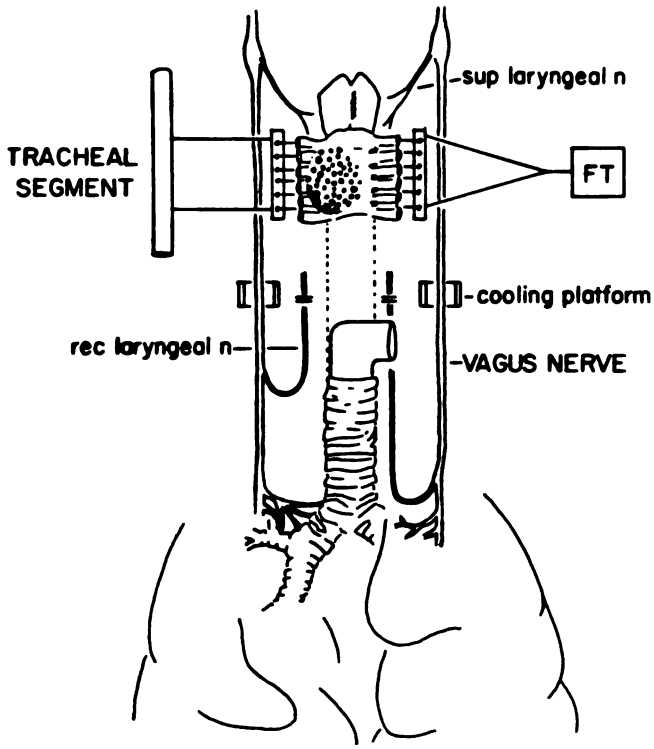

Fig. 2-6. Schematic illustration of the tracheal segment preparation. The segment receives its motor supply from the superior laryngeal (sup laryngeal n) and recurrent laryngeal nerves (rec laryngeal n). After the recurrent laryngeal nerves were cut, any subsequent interruption of the cervical vagus nerves would not affect the motor supply of the segment. The secretion hillocks represented by little dots on the surface of the trachea were recorded on videotape.

through a dissecting microscope, and its image was projected by a television camera (Sony AVC 1400) onto a television screen, together with the output from a time signal generator (AM Datavision DT-1). The image and time signal were recorded by a videotape recorder (Sony VO-2600) for subsequent playback and measurement of the rate of hillock formation. Hillocks with a diameter >0.2 mm were counted in a 0.6 cm^2 field of mucosa, which was displayed on the television screen, counts being made at intervals of 10 sec for 60 sec before and 60 sec after each experimental maneuver.

Protocol

The tracheal segment is innervated by the superior, recurrent, and pararecurrent laryngeal nerves (Fig. 2-6). The recurrent and pararecurrent nerves were cut at the beginning of the experiment so that the tracheal segment received its motor supply solely from the superior laryngeal nerves (Brown et al, 1980). Therefore, cooling or cutting the cervical vagus nerves would interrupt afferent fibers from the thorax but would leave intact the efferent supply to the glands of the segment (Fig. 2-6).

To determine whether stimulation of RARs can reflexly evoke an increase in tracheal submucosal gland secretion, the secretion rates at different levels of RAR activity were compared as follows.

Effects of removal of PEEP and application of NEEP. To stimulate RARs, the lungs was deflated by reducing PEEP to atmospheric pressure, or to a negative end-expiratory pressure (NEEP) by applying a pressure of -4 cm H_2O to the outlet tube of the respirator. The rate of secretion from tracheal submucosal glands was measured at 10-second intervals for 60 sec before and for 60 sec after these maneuvers. As a control, the secretion rate at similar intervals was measured without reducing PEEP.

Effect of decreasing C_{DYN}. To stimulate RARs, C_{DYN} was reduced by restoring PEEP after applying a negative pressure for about 60 sec. The secretion rate was then measured for 2 minutes at 10-second intervals and was compared with that during the control period.

Effect of blocking reflex pathways. To determine whether the increased secretion was mediated by a vagal reflex, the application of NEEP was repeated after both lower cervical vagus nerves were cut or cooled to 6°C (see Vagal Cooling Procedure) to block conduction in myelinated A fibers (PSRs and RARs) but not that in non-myelinated C-fibers. In some cases atropine (1 mg/kg i.v.) was used to determine whether the efferent arm of the reflex was cholinergic.

EFFECTS OF RARs ON BREATHING

In these studies rabbits breathed spontaneously, respiratory airflow being recorded by a pneumotachograph (Fleisch type 1) and a differential pressure transducer (Statham PM15TC) whose signal was integrated (Grass Polygraph 7P10A integrator) to give a record of tidal volume. Inspiratory time (Ti) and expiratory time (Te) were measured from the respiratory flow traces.

Protocol

To examine the relationship between respiratory duration and different inputs from vagal afferents, Ti and Te were measured at different vagal temperatures (37, 15, 10, 7, 5, 3 and 0°C). Values of Ti and Te were averaged over 5 consecutive breaths at each vagal temperature. The cooling procedure used was the same as that described above.

RESULTS

Results are divided into 2 sections: vagal afferent studies and reflex studies.

AFFERENT STUDIES

A total of 72 rapidly adapting receptors (RARs), 87 slowly adapting pulmonary stretch receptors (PSRs) and 6 pulmonary C-fibers were examined in cats, rabbits and dogs. The major effort was devoted to elucidating the effects of decreasing dynamic lung compliance (C_{DYN}) on the impulse activity in the different vagal afferents; RAR studies in cats and rabbits received main emphasis.

LUNG COMPLIANCE

C_{DYN}, measured in 18 rabbits by the experimental methods outlined above, ranged from 4.1 to 7.5 ml/cm H_2O (mean±S.E., 5.5±0.2). These values were very close to those obtained by Crosfill and Widdicombe (1961) in rabbits (range, 3.5-10.8 ml/cm H_2O; mean, 6.0). C_{DYN} measured in 14 cats ranged from 4.7-11.3 ml/cm H_2O (8.0±0.5), values somewhat lower than those obtained by Crosfill and Widdicombe (1961) in

this species (range, 9.9-17.4 ml/cm H_2O; mean 13.4). When the maximal compliance values obtained in the present study were normalized by body weight they averaged 1.4±0.1 and 2.2±0.2 ml/cm H_2O/kg in rabbits and cats, respectively. The relatively lower lung compliance in rabbits than in cats was also noted by Crosfill and Widdicombe (1961).

C_{DYN} was reduced in a stepwise fashion by periodically removing and then replacing positive end expiratory pressure (PEEP). With each maneuver, C_{DYN} decreased on average by about 10% of control (Table 3-1). In some experiments C_{DYN} was recorded for more than 5 minutes after each step. The decrease in C_{DYN} persisted and C_{DYN} remained constant throughout the recording period. In some animals the same procedures were repeated several times, the reduction in C_{DYN} caused by periodic removal of PEEP was fairly repeatable in the same animal from experiment to experiment.

STUDIES ON RARs

Of the 72 RARs examined, 34 were in cats, 32 in rabbits and 6 in dogs. For 27 receptors in cats and 26 receptors in rabbits the response to changes in C_{DYN} were examined in detail, according to the protocol outlined above. The results of these experiments will be described first.

Control Discharge

Under control conditions (with the lungs ventilated at constant tidal volume and rate, and after several large inflations had increased compliance to a maximum), RAR activity was low on average [1.2±0.3, 1.0±0.2 and 1.1±0.7 impulses/sec in rabbits (n=26), cats (n=27) and dogs (n=6), respectively]. In the larger samples of receptors from the rabbit and cat, the distribution of control impulse frequencies was markedly skewed (Fig. 3-1). The majority of receptors in all three species discharged irregularly, although most activity occurred during the inflation phase of the ventilator cycle. Most RARs were fairly inactive and were often silent for several successive ventilator cycles. However, only four receptors (one in a rabbit and three in cats) were completely inactive throughout the 2 minute control period. At the other extreme, five receptors in each species were active in every ventilator cycle, and had discharge rates 2 to 5 times the average value (Fig. 3-1).

In general, the more active a receptor, the more likely was its discharge to have a relatively regular, phasic pattern related to the ventilatory cycle. Seven of 10 active receptors discharged in inflation, although scattered impulses in deflation were not uncommon (Fig. 3-2), and the impulses in deflation were often in time with the heart

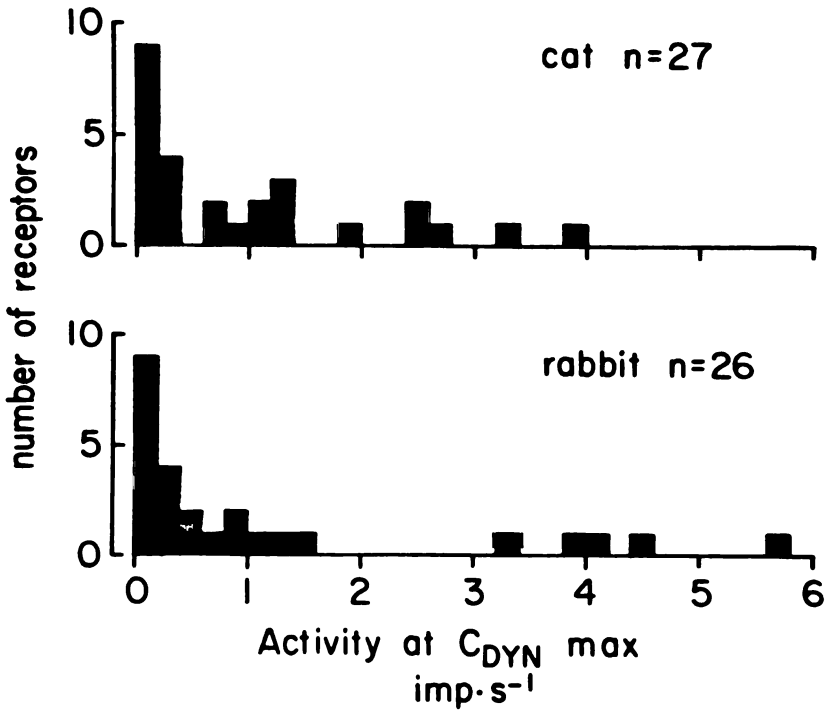

Fig. 3-1. Distribution of control impulse frequencies of 53 rapidly adapting receptors (26 in rabbits, 27 in cats), activity recorded at maximal C_{DYN} and averaged over 5-7 complete ventilatory cycles (approximately 20 sec).

beat. Three receptors (two in rabbits and one in a cat) discharged only in deflation under control conditions (Fig. 3-3). The location of a receptor along the bronchial tree had no obvious influence on the pattern of discharge at high lung compliance. For example, of five receptors located in second order bronchi in cats, three were active and discharged with every lung inflation, and two were relatively inactive and discharged in only occasional cycles, usually during deflation.

Some RARs not only had an obvious respiratory modulation of discharge, they also fired with a cardiac rhythm during the deflation phase of the ventilator cycle (Fig. 3-3). In addition, a few receptors had a prominent cardiac modulation during the inflation phase (Fig. 3-4). In some cases gently lifting the heart so that it was no longer in contact with the lungs caused the cardiac modulation to disappear.

Within the ventilatory cycle there was no close temporal relationship between RAR activity and the maximal rate of change of tracheal pressure (dp/dt). In 5 experiments RAR activity and dp/dt (obtained by differentiating the tracheal pressure signal) were recorded simultaneously. The results showed no close correlation between these two variables either at maximal C_{DYN} or at reduced C_{DYN} (Fig. 3-5), although RAR activity increased after C_{DYN} decreased and the maximal

dp/dt increased.

Effect of Decreasing C_{DYN} During Phasic Lung Inflation

RAR activity during positive pressure ventilation at constant rate and tidal volume was inversely related to C_{DYN}, i.e., directly related to lung stiffness ($1/C_{DYN}$). In all, 23 of 26 RARs in rabbits and 25 of 27 RARs in cats were stimulated as C_{DYN} was reduced (i.e., lung stiffness increased). The activity of most RARs increased progressively with each stepwise reduction in C_{DYN} (Figs. 3-2, 3-6, 3-7 and Table 3-1). Thus, although the amount by which compliance was reduced varied from step to step and from experiment to experiment, the average discharge of the samples of receptors examined in rabbits and cats increased significantly at each step (Table 3-1). At the end of each experimental sequence, RAR activity reverted to control levels when compliance was restored by hyperinflating the lungs with a volume equivalent to 3 or 4 tidal volumes (Fig. 3-2). A decrease in compliance had no consistent effect on the remaining five receptors.

The threshold of the response to decreasing C_{DYN} appeared to be relatively low in both species. Two thirds of all RARs examined were stimulated by the initial reduction in compliance, which amounted on average to only 12-13%, and this initial step evoked a significant increase in

the total activity of both samples of receptors ($P<0.01$, Table 3-1). Except for the 5 unresponsive receptors described above, activity in the remaining receptors was recruited at subsequent steps. At the final step, when the reduction in compliance amounted on average to 44% of control, the total activity of both samples of receptors had increased approximately seven fold ($P<0.0001$, Table 3-1).

The response to reduced compliance (increased lung stiffness) varied widely in the sample of 53 receptors examined in cats and rabbits. A wide variation in sensitivity was also apparent when several receptors were examined in turn in a given animal, the sensitivity of a particular receptor being related neither to the number of experiments performed previously in that animal, nor to the level of basal activity of the receptors (Fig. 3-6).

Pattern of Response

An increasing uniformity of the discharge pattern was the most striking feature of the RAR response to increasing lung stiffness ($1/C_{DYN}$). As compliance was reduced, the sparse and irregular activity characteristic of most RARs during the control period changed to a regular burst of impulses as each inflation reached its peak (Figs. 3-2, 3-3, 3-5 and 3-7). With the exception of the 5 unresponsive afferents, all RARs had developed this uniform pattern

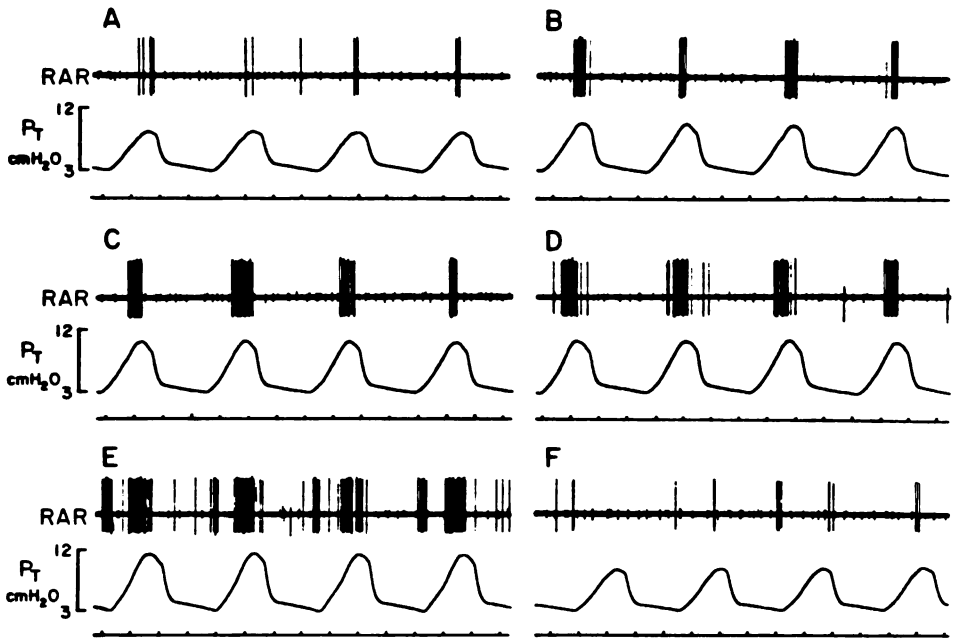

Fig. 3-2. Stimulation of a rapidly adapting receptor in a rabbit by progressive reduction of C_{DYN}. A, control, C_{DYN} maximal; B-E, C_{DYN} successively reduced (see Fig. 2-4, steps B-E), in each case activity being recorded 10 sec after PEEP restored; E, after final reduction, C_{DYN} was 32% less than control; F, after maximal C_{DYN} restored by hyperinflating the lungs. P_T, tracheal pressure; time, 1 sec.

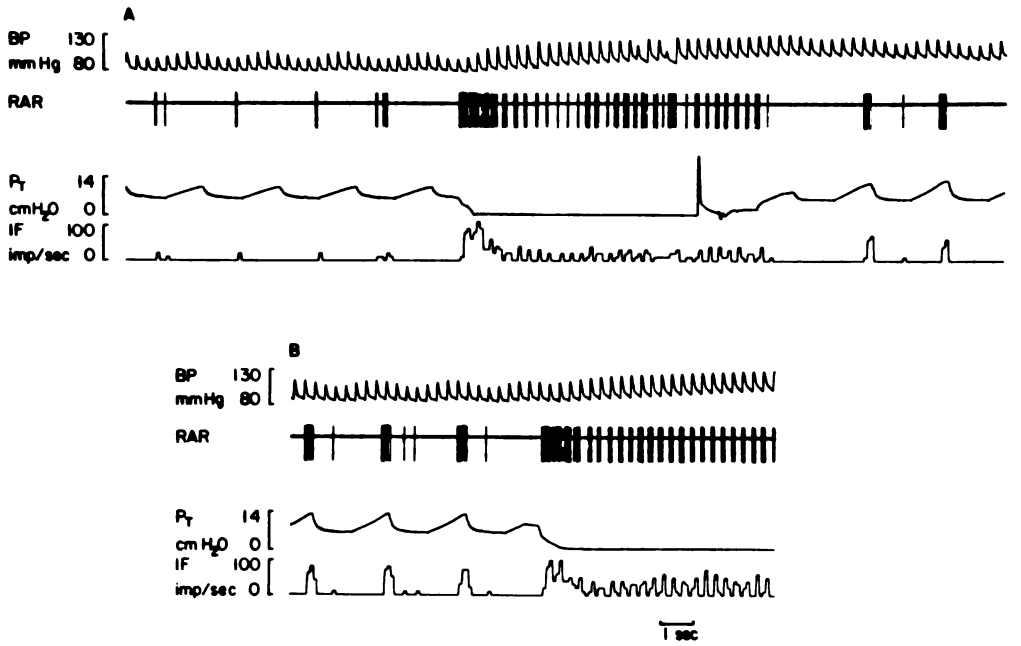

Fig. 3-3. Effect of constant pressure deflation on rapidly adapting receptor (RAR) activity in a rabbit. BP, blood pressure; P_T, tracheal pressure and IF, RAR activity (bin width 0.1 sec). Note at control, RAR fired at low frequency during deflatory phase and the activity was associated with cardiac rhythm. During constant pressure deflation, RAR activity increased, firing with every heart beat. After lung stiffness increased (shown by increase in tracheal pressure), RAR activity incresed with each burst at the peak of tracheal pressure swing. Repeat of constant pressure deflation as lungs became stiffer evoked even higher activity of RAR.

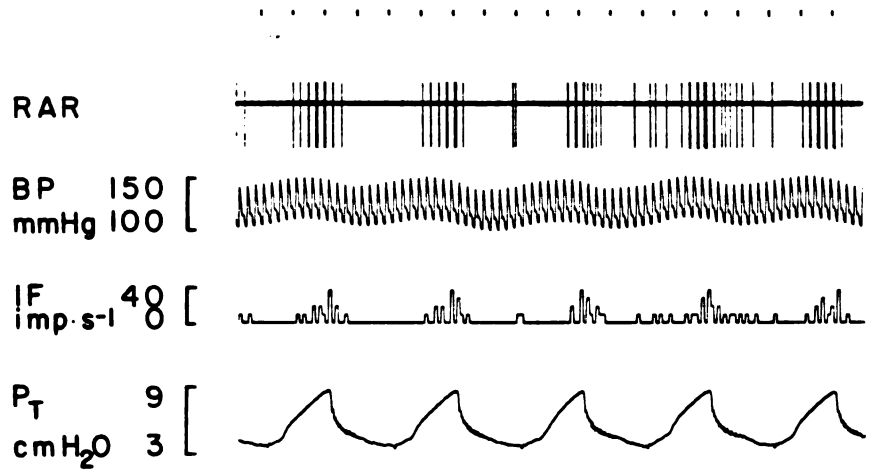

Fig. 3-4. Respiratory and cardiac modulations in a rapidly adapting receptor (RAR) which was located in the upper lobe of the left lung. Note, the cardiac modulation became prominent during inflation. Time trace, 1 sec; RAR, RAR action potentials; BP, arterial blood pressure; IF, RAR impulse frequency (0.1 sec bins) and P_T, tracheal pressure.

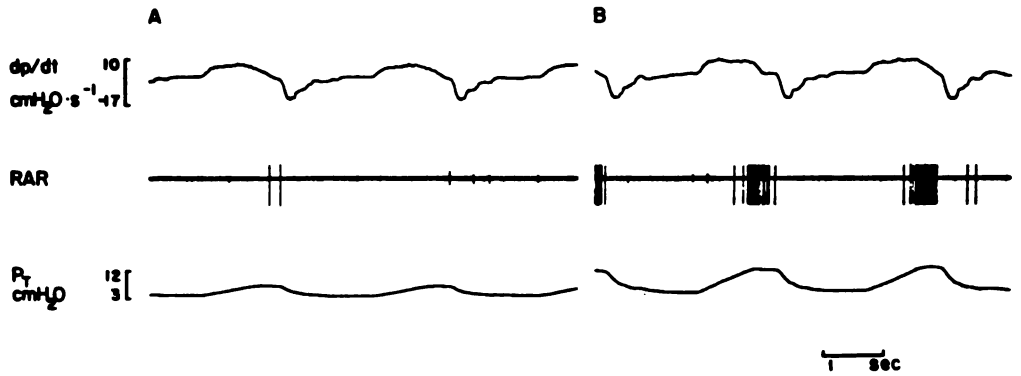

Fig. 3-5. Relationship between RAR activity and rate of change of tracheal pressure (dp/dt). Traces are dp/dt, action potentials of RAR and tracheal pressure (P_T). Note that there was no close temporal relation between RAR activity and maximum dp/dt either during the control period (A) or after lung compliance had been reduced (B).

Rabbits		Cats	
C_{DYN} % control	RAR activity impulses/sec	C_{DYN} % control	RAR activity impulses/sec
100 (control)	1.2 ± 0.3	100 (control)	1.0 ± 0.2
88 ± 1	2.5 ± 0.6	87 ± 1	1.9 ± 0.3
80 ± 2	3.5 ± 0.9	74 ± 3	3.2 ± 0.6
72 ± 2	4.5 ±1.0	67 ± 3	4.9 ± 0.8
59 ± 2	7.7 ± 1.1	59 ± 3	7.8 ± 0.8

Table 3-1. Stimulation of rapidly adapting receptors (RARs) by reduction in dynamic lung compliance (C_{DYN}). Impulse activity (mean ± SE) of receptors (26 in rabbits, 27 in cats) as C_{DYN} reduced in steps. RAR activity averaged over 20 sec during control period when C_{DYN} maximal (100%), and over the first 20 sec after each reduction in C_{DYN}. After each reduction in C_{DYN}, activity was significantly greater than at the preceding level of compliance.

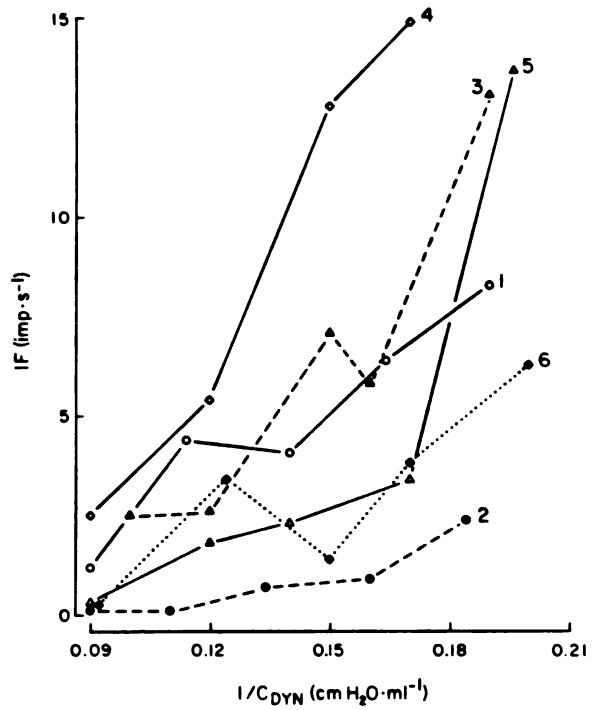

Fig. 3-6. Effect of increasing lung stiffness ($1/C_{DYN}$) on activity of 6 rapidly adapting receptors examined in a single cat. IF, impulse frequency averaged over 20 sec after each reduction in C_{DYN}. Note wide variation in sensitivity of the 6 receptors and lack of correlation between the afferent responses and the order in which the receptors were examined (indicated by numerals 1-6).

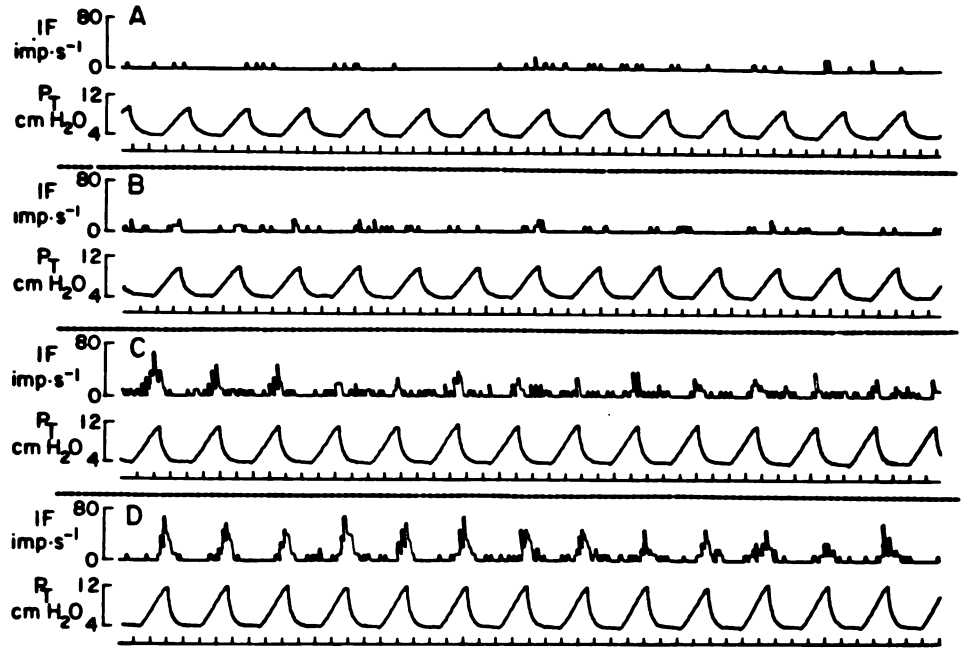

Fig. 3-7. Impulse activity of a rapidly adapting receptor (cat) at 4 levels of lung compliance. A, control, C_{DYN} maximal. B-D, C_{DYN} reduced: B, by 11%; C, by 27%; D, by 35%. IF, impulse frequency recorded by ratemeter in 0.1 sec bins; P_T, tracheal pressure; time, 1 sec. Note increases in both the regularity of discharge pattern and the peak inflation frequency as C_{DYN} reduced. Also note adaptation of the receptor response during the 50 sec period of recording in C and D (each recording began 5 sec after PEEP restored).

of activity when compliance was reduced by 15±3 % in cats and 21±3% in rabbits, peak frequencies averaging 17.0±1.6 and 32.7±3.5 impulses/sec in cats and rabbits, respectively. At the maximal reduction in compliance (see Table 3-1) peak frequencies averaged 58.5±8.9 and 72.8±7.1 impulses/sec in cats and rabbits, respectively. The increase in RAR activity was thus consistent with sensitization to normal, phasic volume inflation. This pattern of activity was in marked contrast to that evoked by removal of PEEP, which was also an effective stimulus to the receptors (see Effect of Deflating the Lungs).

Adaptation of Response

Although lung stiffness remained constant after each removal and restoration of PEEP, the RAR response adapted gradually to reach a new steady state after 50-90 sec (Fig. 3-7). Approximately 10% of the receptors initially stimulated by the first reduction in C_{DYN} reverted to their control level of discharge after 50-90 sec; even so, impulse activity of the whole group of receptors remained significantly above control ($P<0.05$). Overall, adaptation after the various stepwise reductions in compliance averaged 30-50%.

Model of Adaptation

In order to make a better estimate of the adaptation rate of RARs in response to a sudden increase of lung stiff-

ness, linear regression was used to determine the relationship of RAR activity to $1/C_{DYN}$ in each 20-second period after the lung stiffness was abruptly increased. In both cats and rabbits, the RARs responded in a similar manner, the steepest slope was at 10 sec, and the slope became flatter and flatter with time (Fig. 3-8). Each of the regression lines shown in Fig. 3-8 was based on 90 data points in cats (18 RARs), and on 110 data points in rabbits (22 RARs). All the parameters of the regression lines are shown in Table 3-2. The t tests for each slope showed a statistical significance.

From Table 3-2 we can see that in the first 10 sec the relationship between RAR activity and percentage change in lung stiffness had the highest correlation coefficient. With time the correlation coeffecient became smaller and smaller. The decrease in the correlation coeffecient might be due to the background noise of RARs. With time the RAR activity decayed towards its original level, that is, RARs became less active, so that at this time the ratio of signal (activity caused by stimulation) to noise (background fluctuation) decreased, therefore the values of the correlation coefficients became smaller.

To describe the time course of adaptation of RAR discharge mathematically, the successive slopes were fitted into

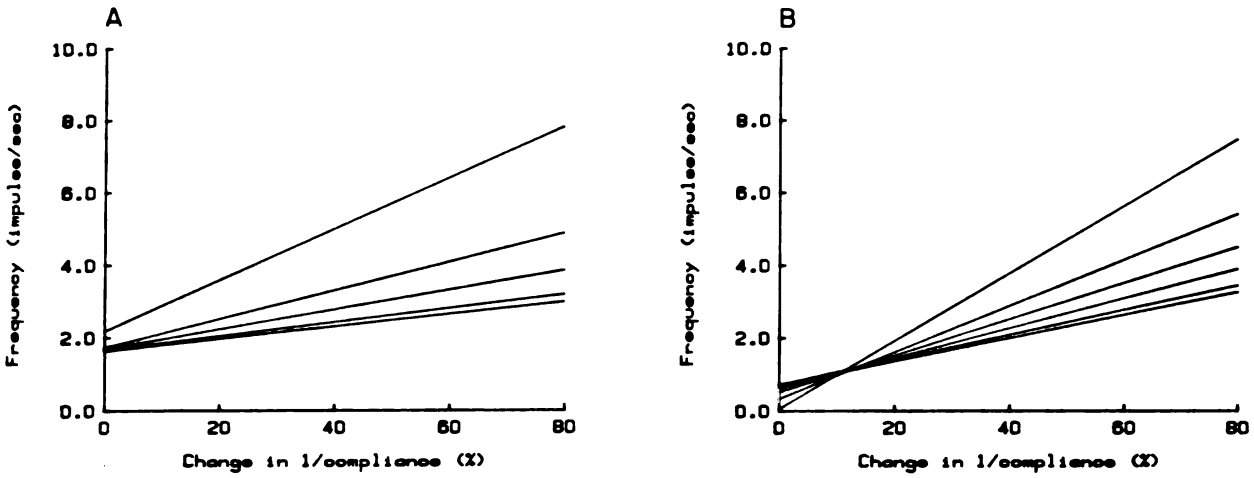

Fig. 3-8. Relationship between firing frequency of rapidly adapting receptors (RARs) and percentage change in lung stiffness ($1/C_{DYN}$) for the cat (A) and rabbit (B). Each line represents a different period of time after the mechanical maneuvers. The regression lines from above down were at 10, 30, 50, 70 and 90 sec respectively. In B, the recording was from 10 to 110 sec.

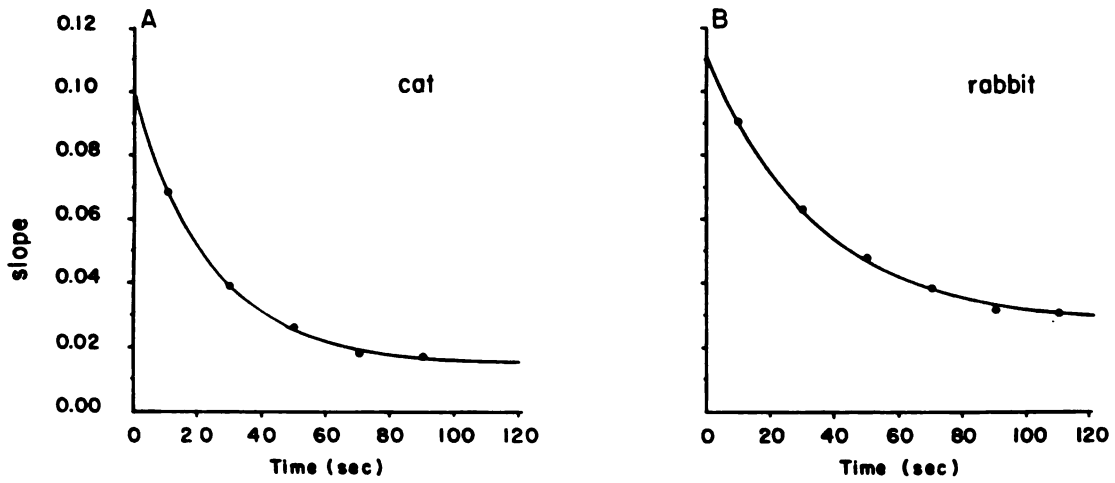

Fig. 3-9. Time course of adaptation of RAR response to increase in lung stiffness ($1/C_{DYN}$). The data points are the slopes obtained from the plot of RAR activity against percentage change of $1/C_{DYN}$. See text for details.

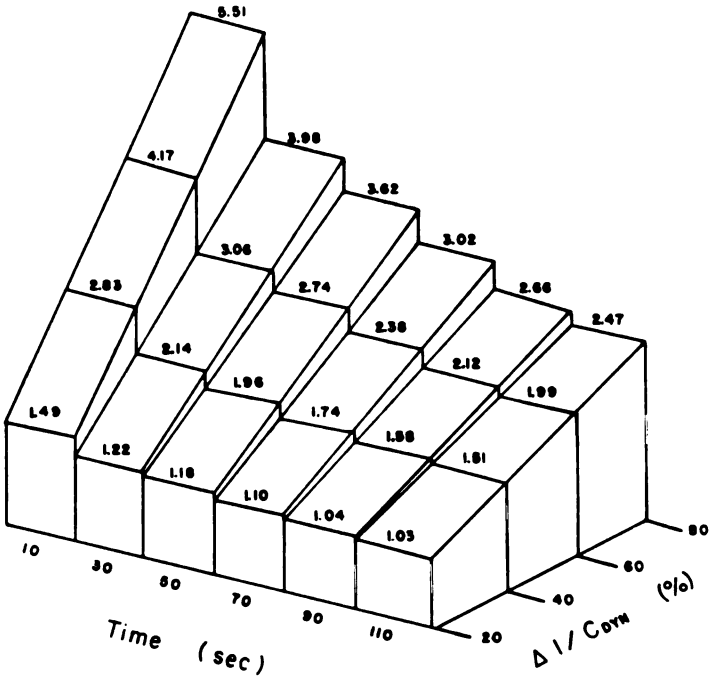

Fig. 3-10. A three dimensional surface chart showing the relation of RAR activity (y axis) to time (x axis) and percentage change of $1/C_{DYN}$ (z axis). The numbers at the top of each box denote RAR activity (impulses/sec). Data obtained from 16 RARs in rabbits.

		Time (sec)					
		10	30	50	70	90	110
Cat	slope	0.070	0.039	0.026	0.019	0.017	
	intercept	2.179	1.728	1.691	1.662	1.631	
	r	0.51	0.40	0.31	0.24	0.23	
	P<	0.001	0.001	0.01	0.05	0.05	
Rabbit	slope	0.092	0.063	0.049	0.041	0.034	0.032
	intercept	0.060	0.337	0.520	0.625	0.722	0.717
	r	0.64	0.57	0.52	0.47	0.40	0.39
	P<	0.001	0.001	0.001	0.001	0.001	0.001

Table 3-2. Time-dependent changes in parameters of linear regression (rapidly adapting receptor activity against percentage change of lung stiffness) in cats and rabbits. The receptor activity was calculated every 20 sec (about 5-7 complete ventilator cycles) for 120 sec after PEEP restored. Note both regression coefficient (slope) and correlation coefficient (r) decreased with time. The P value shows the comparison between a particular r and zero (i.e. no correlation).

an exponential function ($y = y_o e^{-kt} + c$). This form was taken because the slope of the RAR response decayed with time, the rate of decay becoming progressively smaller, reaching a limit after about 110 sec (Fig. 3-8). This limit indicates that after adaptation the RAR activity reached a new steady state, the activity at the steady state being positively related to lung stiffness. By fitting the curve, the adaptation formulae for the cat and rabbit were obtained as follows

$$\text{slope} = 0.0830\, e^{-0.040t} + 0.0147 \text{ (cat)};$$

$$\text{slope} = 0.0842\, e^{-0.029t} + 0.0285 \text{ (rabbit)}$$

In the exponential model adaptation had a half life of 17.3 sec in cats and 23.9 sec in rabbits (Fig. 3-9).

To summarize the RAR response to a sudden increase in lung stiffness, a three dimensional surface chart showing the relationship of RAR activity to both time and percentage change in lung stiffness in the rabbit was constructed (Fig. 3-10). In this figure RAR activity at different stiffness levels was calculated from a series of regression lines.

Effect of Atropine

Theoretically, in experiments of the present design,

removal of PEEP at intervals during artificial ventilation could reflexly evoke a progressive increase in bronchomotor tone, thus leading to an increase in the contribution of flow resistance to the assessment of $1/C_{DYN}$. To examine the possible influence of this factor on RAR response, atropine (1 mg/kg) was given to 4 rabbits and 5 cats. Atropine had no obvious influence on the basal $1/C_{DYN}$, nor on the stepwise increase of $1/C_{DYN}$ induced by removal of PEEP. Moreover, the effect of increasing $1/C_{DYN}$ on 12 RARs examined in these atropine treated rabbits and cats did not differ from that on RARs in untreated animals.

In experiments on another 7 RARs (4 in rabbits and 3 in cats) the experimental sequences were repeated several times before and after atropine, and thus the response of individual receptors in the presence and absence of vagal bronchomotor tone could be compared more accurately. The results not only established the reproducibility of the effects of increasing $1/C_{DYN}$ on individual receptors, but also indicated that vagal bronchomotor tone did not have a major influence under the conditions of the present experiments. The response of 5 receptors was virtually unaltered by atropine (Fig. 3-11 A); that of the remaining two receptors, although diminished by atropine, was still substantial. (Fig. 3-11 B shows the more pronounced example of this effect of atropine.)

Comparison of Increasing Lung Stiffness with Increasing Tidal Volume

The increase in RAR activity observed as the lungs became stiffer was likely to have been causally related to the increase in airway pressure and its rate of change (dp/dt). Therefore, the responses to increasing lung stiffness of 14 receptors (6 in rabbits and 8 in cats) were compared with those to equivalent increases in peak airway pressure and dp/dt induced by increasing the stroke volume of the ventilator without changing its timing, thus increasing tidal airflow. Nine of these 14 RARs were examined after vagal bronchomotor tone had been abolished by administering atropine, or by cutting the vagus nerves above the point of recording.

The 14 RARs tested were stimulated by increasing V_T. Like the response to increased $1/C_{DYN}$, when V_T increased RAR activity usually increased at peak tracheal pressure, exhibiting a similar uniformity of discharge pattern (Fig. 3-12). The RAR activity evoked by increasing V_T also adapted with time (Fig. 3-12). When V_T increased on average from 36.9 ± 1.7 ml (at control) to 55.6 ± 2.2 ml (at the final step of increasing V_T), the change of tracheal pressure during inflation almost doubled (from 5.6 ± 0.4 cm H_2O to 11.1 ± 0.9 cm H_2O). However, RAR activity in the first

10 sec only increased about three to four fold ($P<0.002$).

When RAR responses to increasing $1/C_{DYN}$ and increasing tidal airflow were compared as a function of airway pressure, the response to increasing $1/C_{DYN}$ exceeded that to increasing airflow in all but one instance, in which the two responses were similar (Figs. 3-12 and 3-13 A). For the whole group of 14 receptors, the regression coefficient of impulse frequency on airway pressure was significantly greater for the former mode of stimulation than for the latter (regression coefficients 2.2±0.3 for increasing lung stiffness and 0.8±0.2 for increasing tidal airflow, $P=0.0008$). However $1/C_{DYN}$ did not remain constant, but increased with increasing tidal airflow, either because at high tidal volumes (up to 65 ml in some experiments) the lung was no longer operating on the linear part of its compliance curve, or because the increase in inflation rate caused an increase in the flow resistive component of $1/C_{DYN}$, or both.

When receptor activity was examined as a function of $1/C_{DYN}$ rather than airway pressure, the regression coefficients for the two modes of stimulation were not significantly different (75±12 for increasing lung stiffness and 98±25 for increasing tidal airflow, $P=0.2$; Fig. 3-13 B). The relatively higher responsiveness of RARs in the second group, though not statistically significant, suggest that

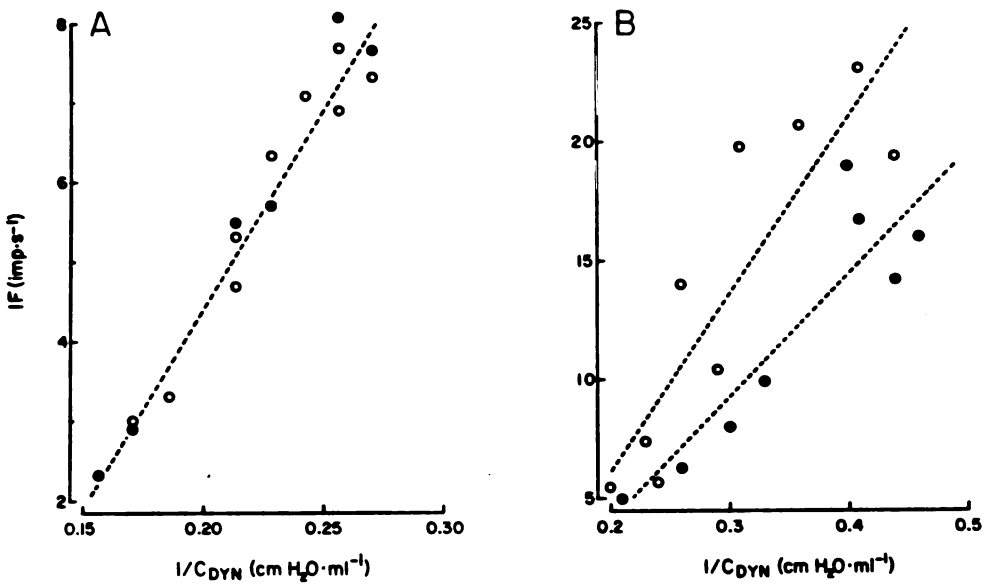

Fig. 3-11. Effect of atropine on responses of 2 rapidly adapting receptors to changes in lung stiffness ($1/C_{DYN}$). IF, impulse frequency averaged over 20 sec after each change in stiffness. Open circles, before atropine; closed circles, after atropine. A, rapidly adapting receptor (cat); results typical of 5 of 7 receptors, the response being unaffected by atropine. B, rapidly adapting receptor (rabbit); results typical of 2 of 7 receptors, the response being reduced but not abolished by atropine.

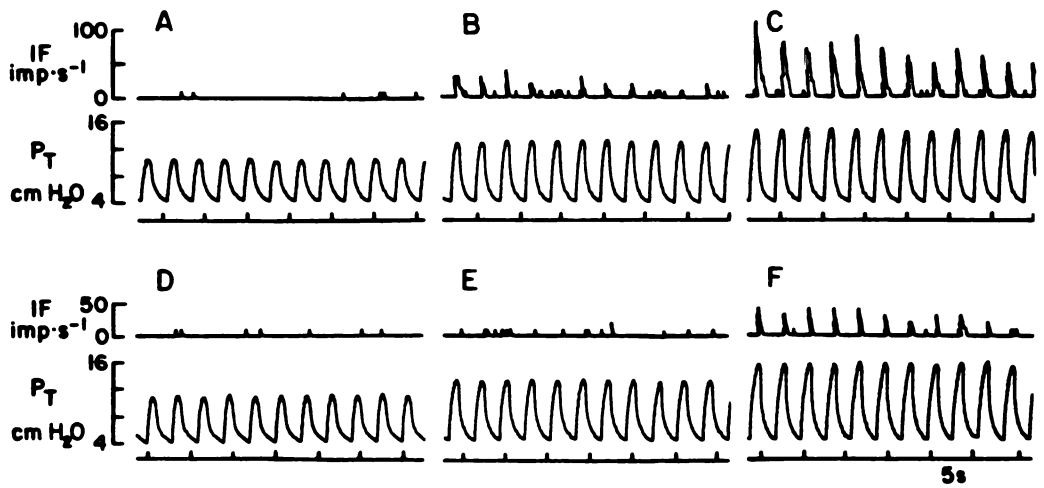

Fig. 3-12. Comparison of responses of a rapidly adapting receptor (cat) to increased lung stiffness (A-C) and increased tidal airflow (D-F). Tidal airflow was increased by increasing ventilator stroke without changing duration of inflation, total cycle length or PEEP. IF, impulse frequency recorded by ratemeter (0.1 sec bins). A and D, control (maximal compliance); B and C, successive increases in lung stiffness; E and F, successive increases in tidal airflow. Note that for approximately equal increases in tracheal pressure (P_T) and dp/dt, the increase in lung stiffness was the more effective stimulus.

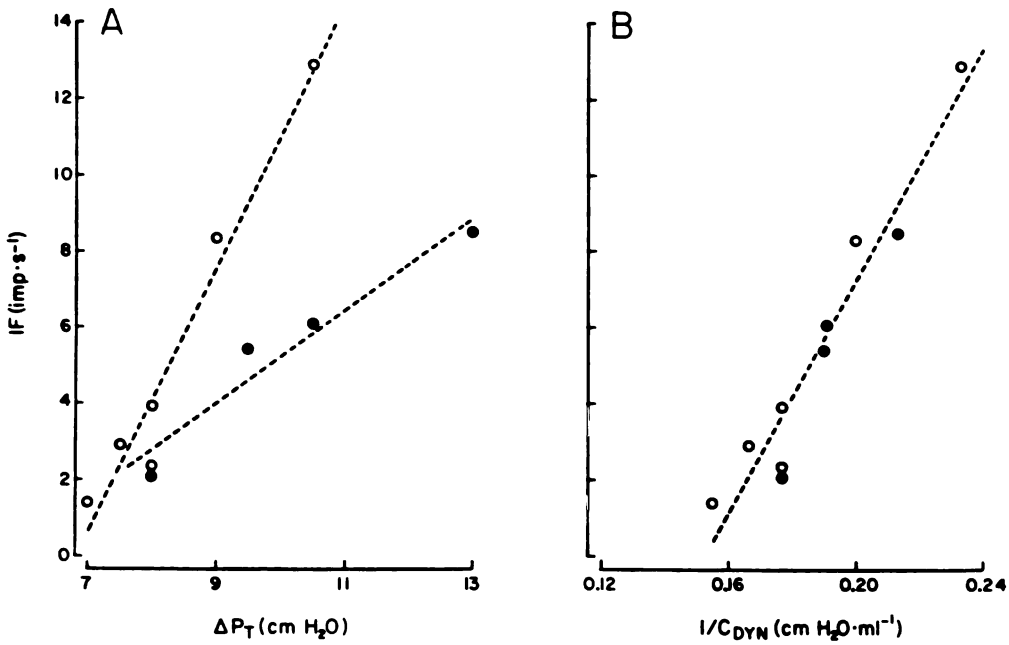

Fig. 3-13. Comparison of responses of a rapidly adapting receptor (cat) to increased lung stiffness (open circles) and increased tidal airflow (closed circles). A, impulse frequency (IF) as function of tracheal pressure (P_T), and B, as function of lung stiffness ($1/C_{DYN}$). See text for further explanation.

tracheal pressure and flow rate are minor factors in stimulating RARs compared with lung stiffness.

Effect of C_{DYN} on Response to Static Lung Inflation

In experiments on 17 RARs (3 in rabbits and 14 in cats), the RAR response to a static lung inflation lasting 10 to 20 sec was examined under control conditions and when the lungs had been made stiffer. The lungs were inflated abruptly from a control end-expiratory pressure of 4 cm H_2O to a pressure of 20 cm H_2O; this was done both before and after $1/C_{DYN}$ was increased by approximately 60% above control (about 40% reduction in C_{DYN}). In all 17 RARs, both the peak discharge and the steady-state discharge were significantly higher ($P<0.01$) when the lungs were stiffer (Figs. 3-14 A, B and 3-15). The Adaptation Index in response to constant pressure inflation was not significantly affected, however (81.9±3.7 and 78.4±4.3 for Adaptation Index during control and high lung stiffness respectively, $P>0.05$).

The response of 5 RARs to static lung inflation to 9-10 cm H_2O for 10-20 sec were also examined. At normal lung compliance, such a moderate degree of inflation, which represents an increase of only 5-6 cm H_2O above the control end-expiratory pressure, has little effect on RARs (Fig. 3-14 C) (Knowlton and Larrabee, 1946). When compliance was reduced,

however, static lung inflation to 9-10 cm H_2O stimulated 3 of the 5 receptors. The discharge evoked by this moderate inflation was irregular and showed little sign of adaptation over the inflation period (Fig. 3-14 D).

Effect of Deflating the Lungs

Most RARs (82%) were strongly stimulated by removal of PEEP or application of negative end expiratory pressure (NEEP). The response was positively related to the degree of deflation, that is to say, the stronger the deflating force applied the more active the receptors ($P<0.05$; Table 3-3). During removal of PEEP or application of NEEP, RAR activity usually became dispersed and occurred during the deflation phase, often with a prominent cardiac modulation (Fig. 3-16). This shift of RAR activity in relation to the ventilation phase and the occurrence of a cardiac modulation are consistent with the observations of Armstrong and Luck (1974) in cats and Sampson and Vidruk (1975) in dogs.

In a study of 5 RARs the ventilator was stopped to keep the lungs deflated either at PEEP or at 0 cm H_2O. The receptors responded initially with a high impulse discharge, which then declined rapidly (Fig. 3-3). During the maintained deflation, the respiratory modulation disappeared and the cardiac modulation of receptor activity became

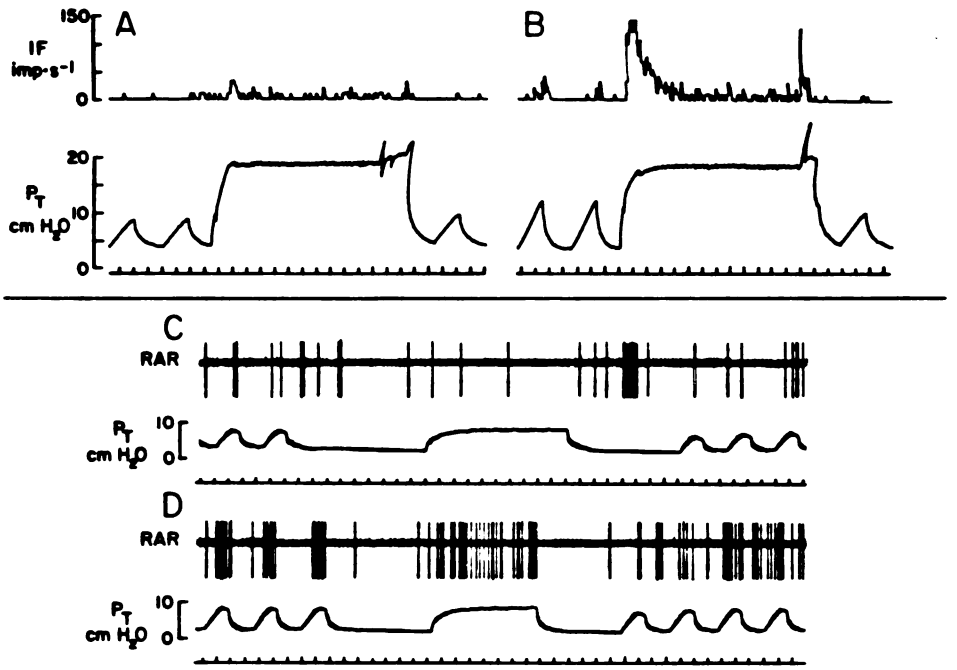

Fig. 3-14. Effect of lung compliance on rapidly adapting receptor response to two levels of static lung inflation; 2 receptors (A, B, and C, D) examined in different cats. A, B, impulse frequency recorded by ratemeter (0.1 sec bins); lungs inflated to 20 cm H_2O for 13 sec. A, C_{DYN} maximal. B, after C_{DYN} reduced by 47%; note adaptation and increases in both initial and steady state responses. C, D, action potentials recorded; lungs inflated to about 9 cm H_2O (i.e., to a pressure equal to that at peak of normal tidal volume inflation) for 7-10 sec. C, C_{DYN} maximal; note irregular discharge. D, after C_{DYN} reduced by 30%; receptor now fired with each phasic inflation and showed little evidence of adaptation during moderate static lung inflation. Abbreviations as in previous figures; time, 1 sec.

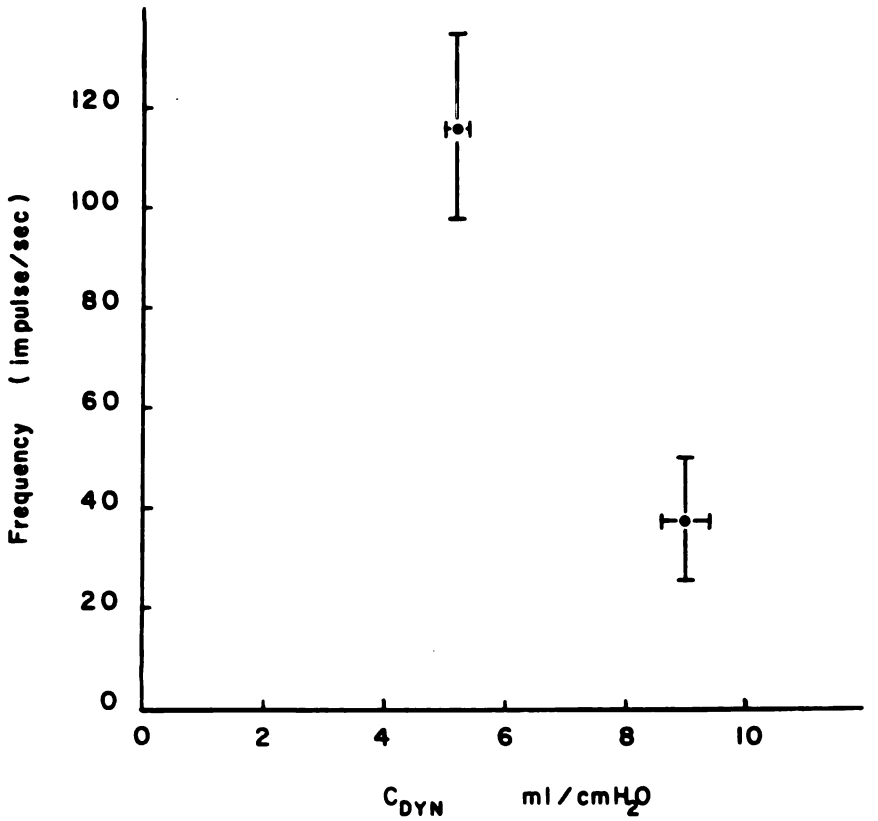

Fig. 3-15. Peak frequencies of rapidly adapting receptors (n=14) during constant pressure inflation at two levels of C_{DYN} in cats. Note that after C_{DYN} decreased by 40%, the peak frequency increased threefold ($P<0.001$). Data are presented as mean ± SE.

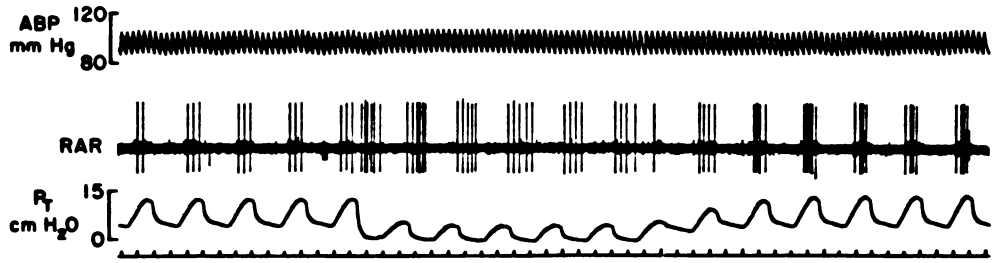

Fig. 3-16. Removal of PEEP stimulates a rapidly adapting receptor (cat) and alters its pattern of discharge. Receptor fired in inflation when PEEP present, and in deflation when PEEP removed. Note also that when PEEP finally restored to control level, tracheal pressure at peak of inflation was 0.5 cm H_2O above the control level; hence the lungs were stiffer and the receptor fired more vigorously than in the control period. ABP, arterial blood pressure; other abbreviations as in previous figures; time, 1 sec.

	Afferent activity (impulses/sec)			
Receptor	Control	$C_{DYN}\downarrow$	PEEP off	NEEP applied
RARs	1.1 ± 0.7	2.2 ± 0.8*	2.6 ± 0.9*	4.5 ± 1.2*
PSRs	23.2 ± 9.9	21.7 ± 8.2	11.4 ± 6.1*	11.2 ± 5.1*
C-fibers	0.6 ± 0.2	0.9 ± 0.2	0.6 ± 0.3	0.5 ± 0.1

Table 3-3. Vagal afferent activities (impulses/sec) in dogs recorded at 4 experimental conditions: control; decreasing dynamic lung compliance (C_{DYN}) by 40%; removing positive end expiratory pressure (PEEP off) and application of negative end expiratory pressure (NEEP applied). Six receptors in each category: rapidly adapting receptors (RARs), slowly adapting pulmonary stretch receptors (PSRs) and C-fibers. Values are means ± SE (impulses/sec), averaged over 2 minute experimental period. Asterisks denote statistical significance of difference from control value ($P<0.05$).

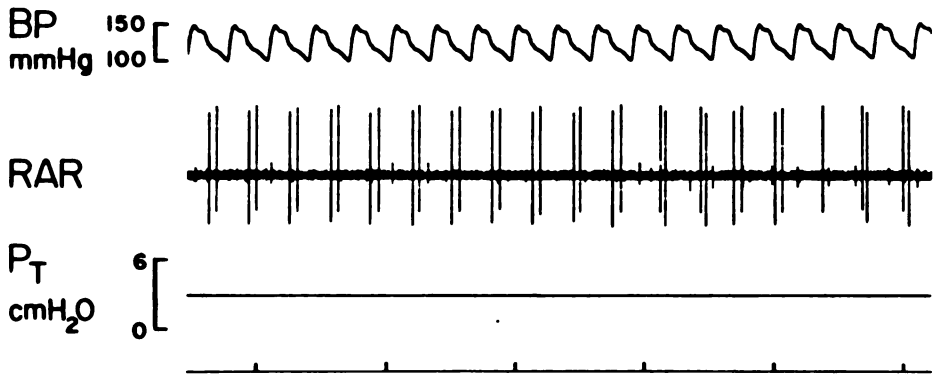

Fig. 3-17. Cardiac modulation of rapidly adapting receptor (RAR) activity at constant PEEP (ventilator turned off). BP, blood pressure; RAR, RAR action potentials; P_T, tracheal pressure; time, 1 sec. Note RAR activity was associated with each heart beat before the systolic increase in blood pressure.

prominent. The receptors fired with each heart beat, usually just before the systolic increase in blood pressure (Figs. 3-3; 3-17). Furthermore, when the ventilator was stopped, RAR activity was also positively related to lung stiffness (Fig. 3-3). The stiffer the lungs, the more active the receptor at constant pressure deflation.

Effects of Histamine

RARs are stimulated by histamine. In order to determine whether the stimulation of RARs by histamine can be ascribed to an increase in lung stiffness, 19 RARs (6 in rabbits and 13 in cats) were examined. The responses induced by a bolus injection of 50 μg/kg histamine into the right atrium were compared with those produced by increasing lung stiffness (for the details of the experimental procedure, see METHODS).

The results from all the 19 RARs examined showed that, for comparable increases in lung stiffness, maximal RAR activity was higher after histamine than when lung stiffness was increased (Table 3-4). This suggested that the changes in lung mechanics after histamine injection could not fully explain the increased RAR activity, and that some other factor or factors must have been involved.

In cats, the maximal stimulation of RARs by histamine

occured long after the maximal increase in lung stiffness. Only 2 of the 13 receptors were activated within 3 sec, the majority of receptors not being activated until 6 sec after injection of histamine. Activity did not reach a peak until an average of 24.7 sec after injection. By contrast, tracheal pressure began to increase about 3 sec after injection, and reached its peak on average at 10.8 sec after injection (Table 3-4).

In experiments on 12 RARs in cats, the receptor activity at the maximal tracheal pressure after histamine injection was compared with the activity evoked by decreasing dynamic lung compliance. For similar increases in tracheal pressure receptor activities were not significantly different (Figs. 3-18 A, B and Table 3-4). However, after histamine injection RAR activity continued to increase and reached its peak approximately 14 sec after tracheal pressure reached a maximum. The activities at these two times were significantly different ($P<0.05$; Table 3-4).

After histamine injection, cardiovascular variables also changed. At first histamine appeared to have a prominent vasodilator effect. Mean blood pressure began to decrease, usually after about 3 sec; after about 23 sec it increased gradually, often to a level above control (Fig. 3-19). Pulse pressure also increased significantly beginning about 10

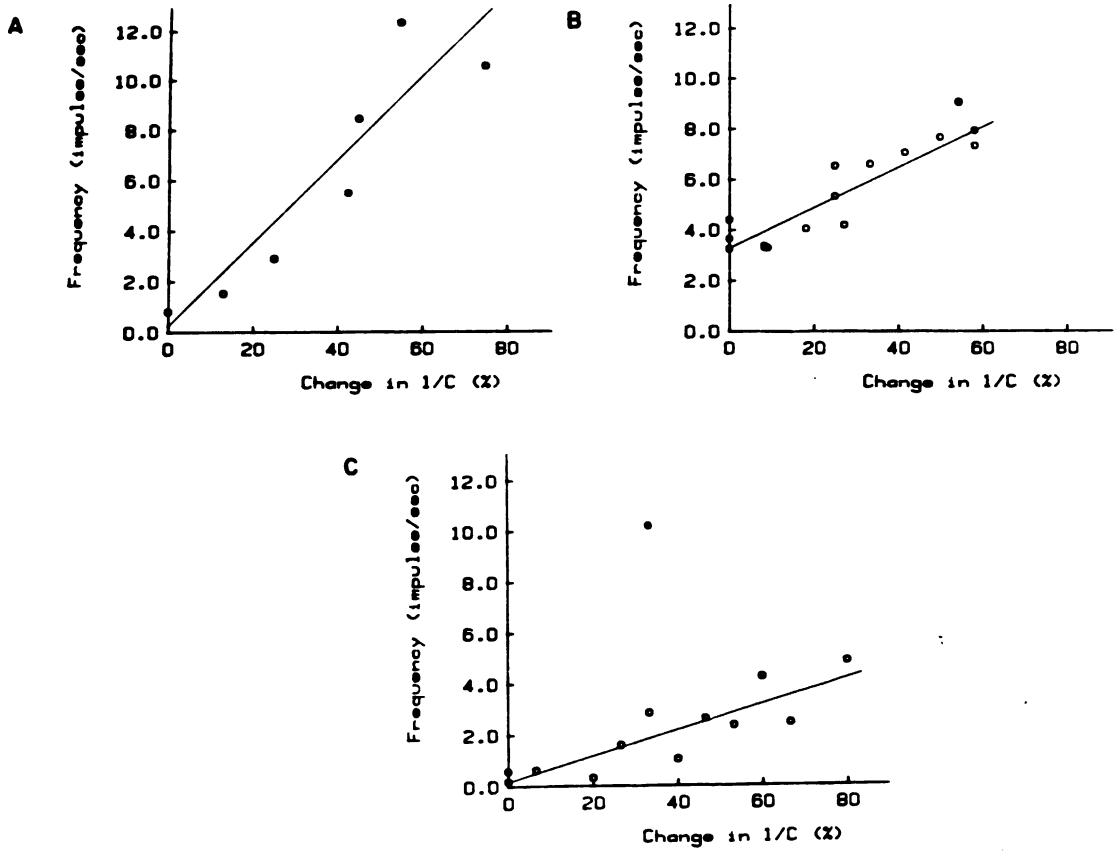

Fig. 3-18. Responses of three rapidly adapting receptors (RARs) to an increase in stiffness (1/C) produced by briefly removing PEEP (open circles) or by injecting histamine (50 μg/kg) into the right atrium (closed circles). Two of the receptors were in cats (A, B) and one in a rabbit (C). The data points after histamine were calculated over the three consecutive ventilatory cycles with the largest increases in tracheal pressure (i.e. the maximal increase in lung stiffness). Linear regression lines were calculated for the open circles data. Note, in the cat RAR activity induced by histamine was comparable with that induced by increasing 1/C; however, in the rabbit RAR activity induced by histamine exceeding that induced by simply increasing 1/C.

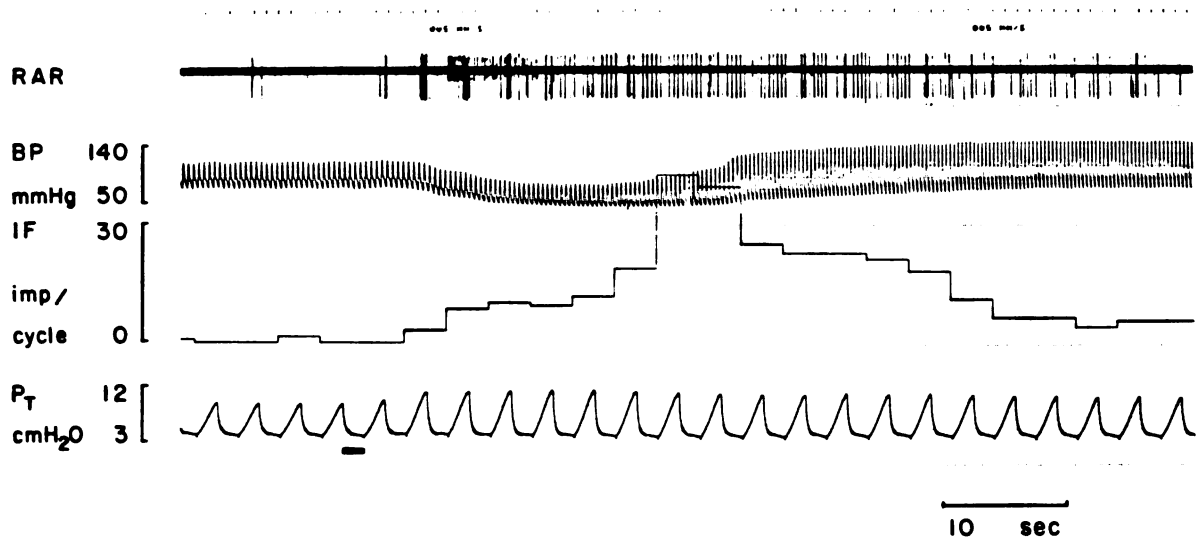

Fig. 3-19. Effect of right atrial injection of histamine (50 μg/kg) on rapidly adapting receptor (RAR) activity in a cat. RAR, RAR action potentials; BP, blood pressure; IF, ratemeter counts of RAR activity in each ventilator cycle; P_T, tracheal pressure and injection marker (black bar). Note RAR activity increased initially with a respiratory modulation, then with a prominant cardiac modulation superimposed on the respiratory one. Also note the response of a bronchial C-fiber (small spikes) at longer latency.

	Impulse frequency (impulses/sec)			latency (sec)	
	Calculated	At Peak P_T	Maximal	To peak P_T	To maximal IF
Cat	5.2 ±1.4	5.2 ± 1.2	7.2 ± 1.5* ~	10.8 ± 1.3	24.7 ± 3.5
Rabbit	1.9 ± 0.4	6.1 ± 2.1*	8.4 ± 2.7* ~	14.0 ± 1.5	18.7 ± 3.7

Table 3-4. Effects of right atrial injection of histamine (50 μg/kg) on RAR activity of 13 RARs (cat) and 6 RARs (rabbit). Calculated, RAR activity calculated from linear regression (RAR activity against lung stiffness) at the same lung stiffness as that induced by histamine injection; At peak P_T, the RAR activity averaged over 3 ventilator cycles during the maximal increase in tracheal pressure after histamine injection; Maximal, the highest RAR activity averaged over 3 ventilator cycles after histamine injection; To peak P_T, the latency from injection to maximum increase in tracheal pressure (sec); To maximal IF, the latency from injection to maximum RAR activity (sec). * denotes ($P<0.05$) when compared with calculated frequency. ~ denotes ($P<0.05$) when compared with the frequency at peak P_T.

sec after mean pressure decreased (Fig. 3-19).

In all 12 RARs the histamine induced activity had a significant cardiac rhythm (Fig. 3-19) which was superimposed on the respiratory modulation. Like the cardiac modulation of RARs during lung deflation, the receptors usually fired before the systolic increase in blood pressure. The activity did not always occur with each heart beat, however.

The general effect of histamine on 6 RARs in rabbits was similar to that in cats (Table 3-4). All 6 RARs in rabbits showed a cardiac modulation after histamine. RAR activity usually reached its peak 18.7 sec after injection of histamine, while tracheal pressure usually reached its peak 14 sec after injection. As in cats, maximal RAR responses to histamine in rabbits was significantly higher ($P<0.05$), and occurred later than the activity recorded at the maximal increase in tracheal pressure. However, the major difference between the responses of RARs in the two species was that in rabbits RAR activity during the maximal increase in tracheal pressure was higher than that evoked by decreasing lung stiffness at the same tracheal pressure change ($P<0.05$; Fig. 3-18 C and Table 3-4).

STUDIES ON PSRs

Eighty seven PSRs were examined (39 in cats, 42 in rabbits and 6 in dogs).

Control Discharge

The control activity of PSRs, averaged over the ventilator cycle, was 34.5±3.5, 26.2±2.9 and 23.2±9.9 impulses/sec in cats, rabbits and dogs, respectively. Results were analysed and compared in detail for cats and rabbits, in which the samples of PSRs examined were relatively large.

The proportion of 'high threshold' PSRs (PSRs with a clear pause in activity in deflation) and 'low threshold' PSRs (PSRs firing continuously throughout the ventilator cycle) was different in cats and rabbits. In cats the number of high and low threshold PSRs was approximately equal, whereas in rabbits high threshold PSRs outnumbered low threshold PSRs by approximately 2 to 1 (Table 3-5). This difference in the proportion of low and high threshold PSRs in the two species agrees well with the results of other investigators (Kohl et al, 1986; Paintal, 1965). The mean, peak and minimal activities of high and low threshold PSRs are given in Table 3-6.

Effect of Decreasing C_{DYN}

The mean activity of PSRs in cats and rabbits did not change significantly when C_{DYN} was reduced by 42.6±0.3%. The same was true of 6 PSRs in dogs (Table 3-3). The response of individual PSRs in cats and rabbits varied, and the proportions of fibers whose mean activity increased or decreased when C_{DYN} decreased was different in the two species. In cats the activity of about one third of fibers increased and two thirds decreased in response to decreased C_{DYN}; in rabbits the opposite was true, i.e. the activity of two thirds increased and one third decreased. In both species the proportion of fibers whose discharge increased and decreased was the same for both high and low threshold receptors (Table 3-5). The change in PSR activity was small, and 85% of the change was within 10 impulses/sec (Fig. 3--20). However, the activity of three PSRs (one in a cat and two in rabbits) ceased completely when C_{DYN} was decreased, and was restored when compliance was restored to the control level.

The effect of progressive decreases in C_{DYN} was examined in 27 of the PSRs in cats and in 20 in rabbits. Again, the effect was not consistent, and the average mean activity of the group did not show a significant change at any level of C_{DYN} (Fig. 3-21).

Because PSRs are known to have a phasic reflex influence in each respiratory cycle, it seemed important to examine the possible effect of decreasing C_{DYN} on the pattern of activity, as well as on the mean frequency of discharge averaged throughout the cycle. Although the mean activity did not change significantly, the firing pattern of PSRs changed when C_{DYN} was decreased. Thus when C_{DYN} decreased in most PSRs in both cats and rabbits activity increased at the peak of inflation, and decreased in deflation. In 5 PSRs the opposite was true, i.e. when lung compliance decreased activity at peak inflation decreased and activity in deflation increased. For the group as a whole, however, the increase in peak activity and decrease in deflation activity was statistically significant ($P<0.001$; Fig. 3-22).

The higher firing frequency during inflation and the lower frequency during deflation in low threshold PSRs as the lungs became stiffer is illustrated in Fig. 3-23. Thus the firing pattern of 23% of the low threshold PSRs was converted by increasing lung stiffness to the firing pattern of high threshold PSRs, i.e. their activity began after the onset of inflation and was confined to inflation. Similarly, in high threshold PSRs the firing frequency during inflation increased and the silent period during deflation was prolonged (Fig. 3-24).

Comparison of Increasing Lung Stiffness with Increasing Tidal Volume

In experiments on 14 PSRs in cats, the effects of a stepwise increase in $1/C_{DYN}$ and a stepwise increase in tidal volume were compared by calculating the linear regression coeffecient of mean PSR activity relative to the change of tracheal pressure. The effects of increasing lung stiffness were variable; 6 of the 14 PSRs had a positive regression coeffecient, whereas the remaining 8 PSRs had a negative regression coeffecient. By contrast, all 14 PSRs increased their mean discharge in response to a stepwise increase in tidal volume. (Fig. 3-25). For a given change in transpulmonary pressure, the difference in the effectiveness of the two modes of stimulation was significant ($P<0.01$).

When peak activity rather than mean activity of PSRs was plotted against the change of tracheal pressure, 12 of the 14 receptors showed a positive regression coefficient in response to increasing $1/C_{DYN}$, and all receptors showed a positive response to increasing V_T. The difference between the peak responses of PSRs to the two modes of stimulation was not statistically significant (3.1±0.9 and 4.1±0.5 impulses/sec per cm H_2O increase in tracheal pressure for increasing $1/C_{DYN}$ and increasing V_T, respectively).

The increase in lung stiffness induced by periodically

removing and then replacing PEEP was likely to have been due to the collapse of small airways, hence PSRs located in the collapsed region could not sense the gross change in tracheal pressure. I therefore selected only those PSRs with a positive response to a stepwise increase in $1/C_{DYN}$ (i.e., 6 of the 14 receptors) and compared their responses (in terms of mean activity) to the two different modes of stimulation. The results for this population showed no significant difference for the paired sets of data. The mean ± SE of the regression coeffecients was 2.4 ± 1.2 impulses/sec per cm H_2O for increasing lung stiffness and 2.6 ± 0.3 impulses/sec per cm H_2O for increasing tidal volume.

The sensitivity of PSRs to an increase in tracheal pressure produced by increasing V_T was small and sensitivity did not vary markedly between receptors (Fig. 3-25). The receptors increased their mean activity by about one to three spikes for each one cm H_2O increase in tracheal pressure (Fig. 3-25) with a mean±SE of 2.6±0.3 impulses/sec·cm H_2O. These results in cats and rabbits are similar to those obtained by other investigators in dogs (Pack et al, 1986).

Effect of Deflating the Lungs

All the PSRs in cats and rabbits responded to short periods of removal of PEEP (2 to 10 ventilator cycles)

		HT		LT	
		Number	Percent	Number	Percent
Cat	Total	19	100	20	100
	Increased	7	36.8	6	30
	Decreased	12	63.2	14	70
Rabbit	Total	28	100	14	100
	Increased	19	67.8	10	71.4
	Decreased	9	32.2	4	28.6

Table 3-5. Proportion of high threshold (HT) and low threshold (LT) PSRs in cats and rabbits and direction of change in mean activity in response to reduction of C_{DYN}. C_{DYN} was reduced on average by 42.6±0.3 %.

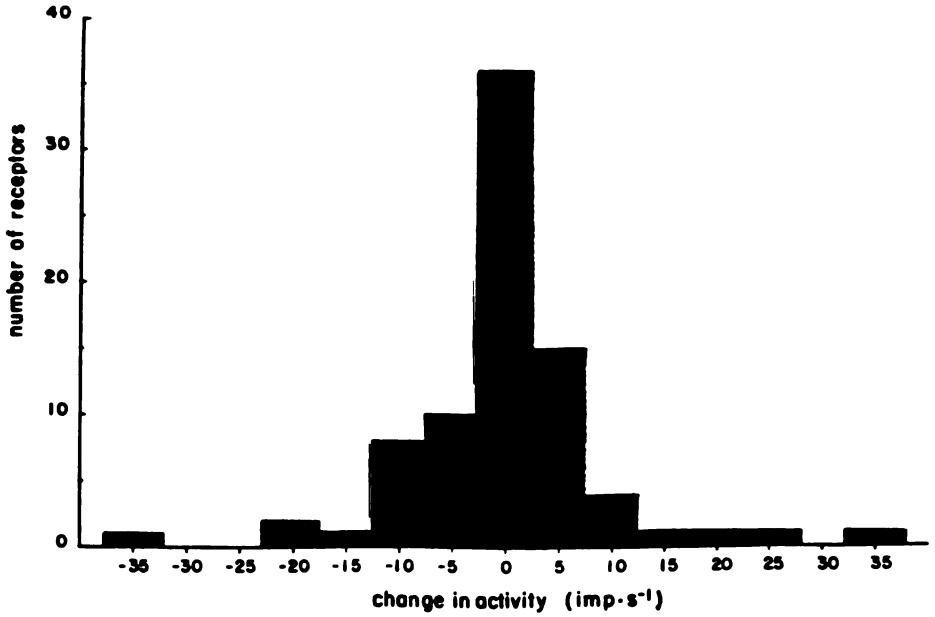

Fig. 3-20. Distribution of the change in mean activity of 81 slowly adapting pulmonary stretch receptors (42 in rabbits, 39 in cats) after C_{DYN} decreased by 42.6%. Activity was averaged over 5-7 complete ventilatory cycles (approximately 20 sec). Note that in approximately half the receptors the absolute increase or decrease in mean activity was 2.5 impulses per sec or less.

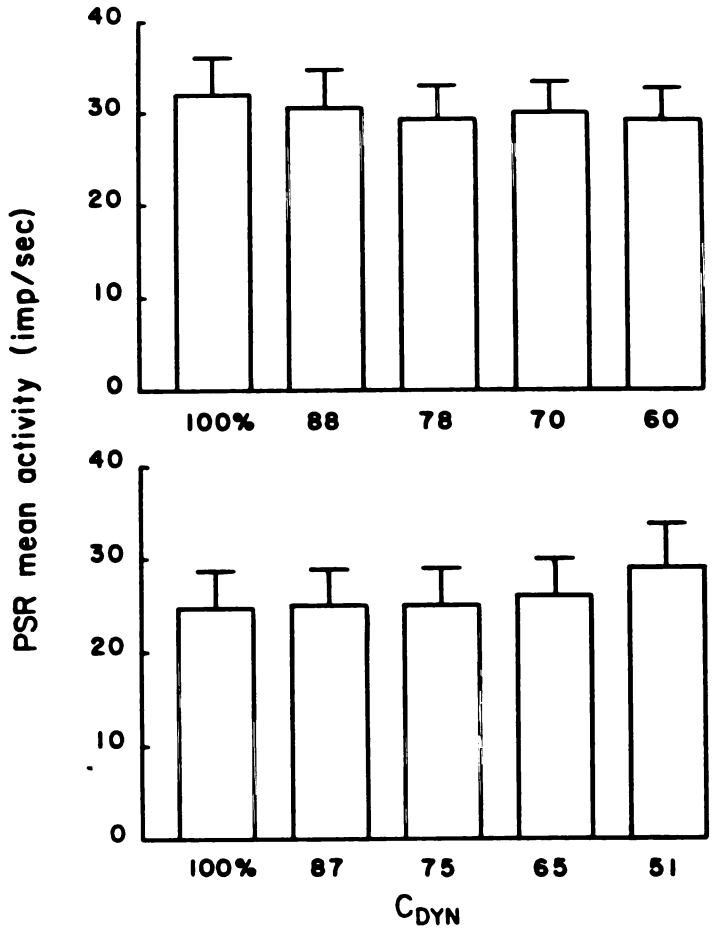

Fig. 3-21. Effect of stepwise decreases in C_{DYN} on the mean activity of slowly adapting pulmonary stretch receptors in cats (n=27; above) and rabbits (n=20; below). Data are means ± SE. Successive mean activities were not significantly different from control.

	PSR type	n	Impulse frequency (impulses/sec) Mean	Maximal	Minimal
Cat	HT	19	18.8 ± 2.5	45.6 ± 3.7	*
	LT	20	49.5 ± 4.3	66.8 ± 5.5	33.8 ± 4.1
Rabbit	HT	28	18.4 ± 2.2	58.2 ± 5.7	*
	LT	14	41.8 ± 5.5	75.5 ± 8.6	18.0 ± 4.2

Table 3-6. Background activity of high threshold (HT) and low threshold (LT) slowly adapting pulmonary stretch receptors (PSRs) in artificially ventilated cats and rabbits. Values are means ± SE. The mean and peak activities were expressed as impulses/sec, averaged over 5 consecutive ventilator cycles. In each ventilator cycle the highest frequency during 0.1 sec was taken as peak activity in that cycle. The minimal activity in HT PSRs was expressed as impulses/sec, calculated over the lowest activity in 0.4 sec during deflation. The * in the rows of LT PSRs was the silent period of PSR activity during deflation. The duration of the silent period for LT PSRs was 2.1±0.4 sec for cats and 1.3±0.1 sec for rabbits.

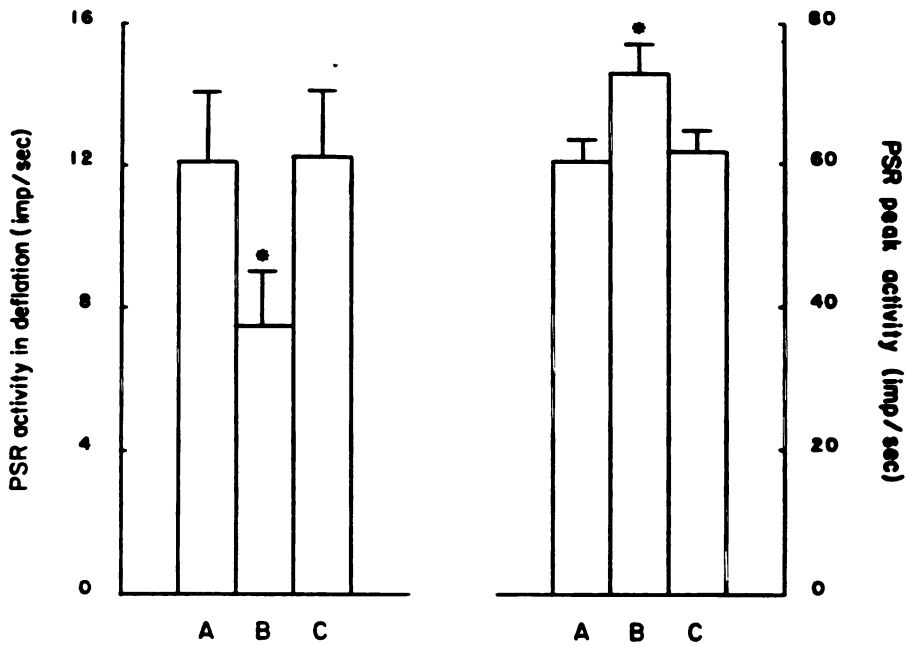

Fig. 3-22. Effects of decreasing C_{DYN} on deflation (left) and peak inflation (right) activities of slowly adapting pulmonary stretch receptors (PSRs) (n=81) in rabbits and cats. A, control; B, decreased C_{DYN} by 42.6%; C, after C_{DYN} restored. * denotes significant difference from control ($P<0.05$).

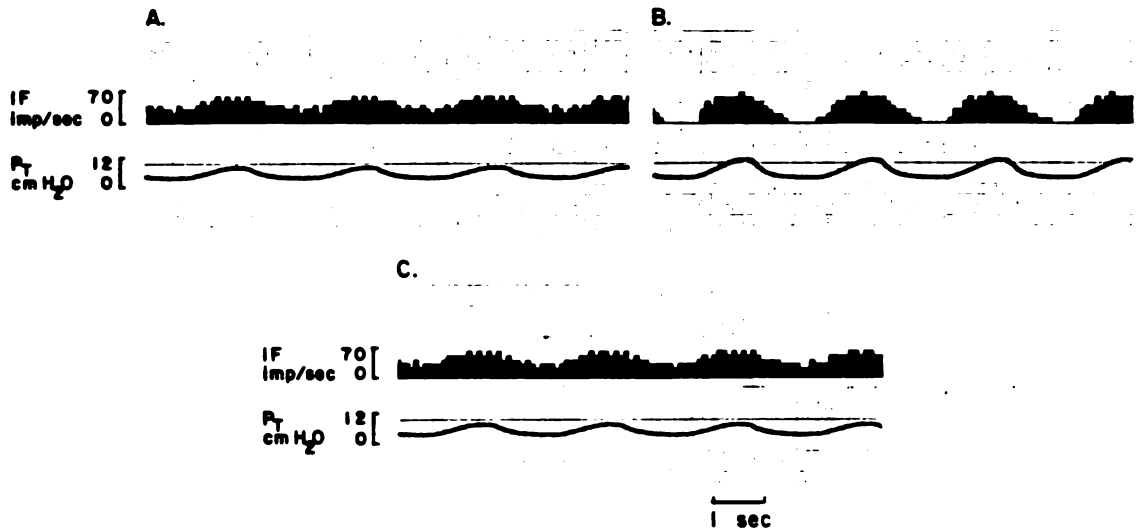

Fig. 3-23. Effect of decreasing C_{DYN} on the activity of a slowly adapting pulmonary stretch receptor (PSR) in a cat. IF, impulse frequency of PSR (0.1 sec bins); P_T, tracheal pressure. A, control; B, decreased C_{DYN}; C, after restoring C_{DYN}. Note, in B, when C_{DYN} decreased the peak activity increased, however, the activity during deflation decreased so much that the receptor became silent for a short period, i.e. the discharge pattern shifted from 'low threshold' to 'high threshold'.

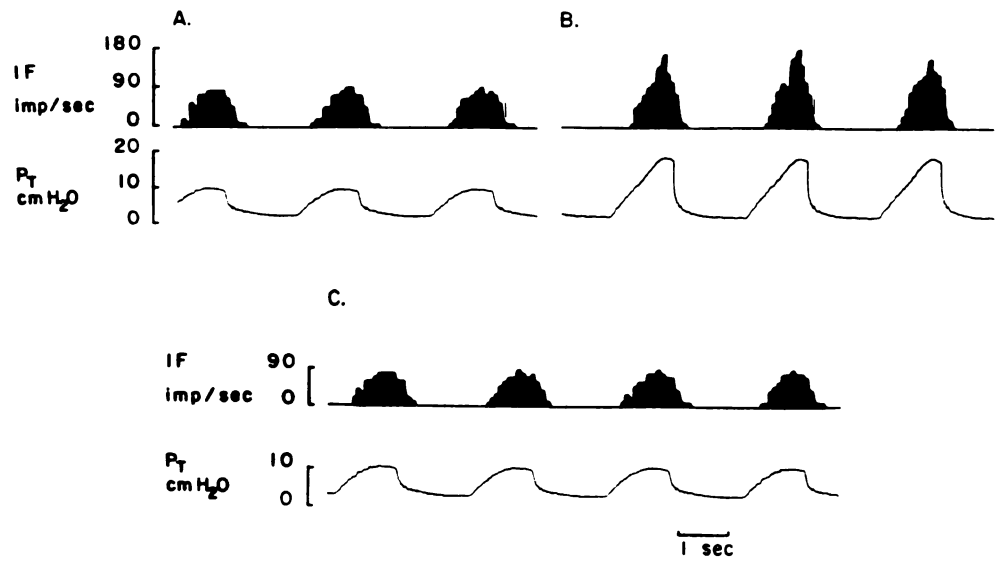

Fig. 3-24. Effect of decreasing C_{DYN} on a high threshold PSR in a rabbit. Abbrivations are the same as Fig. 3-23. Note, in B, when C_{DYN} decreased the peak activity during inflation increased; whereas, the activity during deflation decreased, which is manifasted by the prolongation of the silent period.

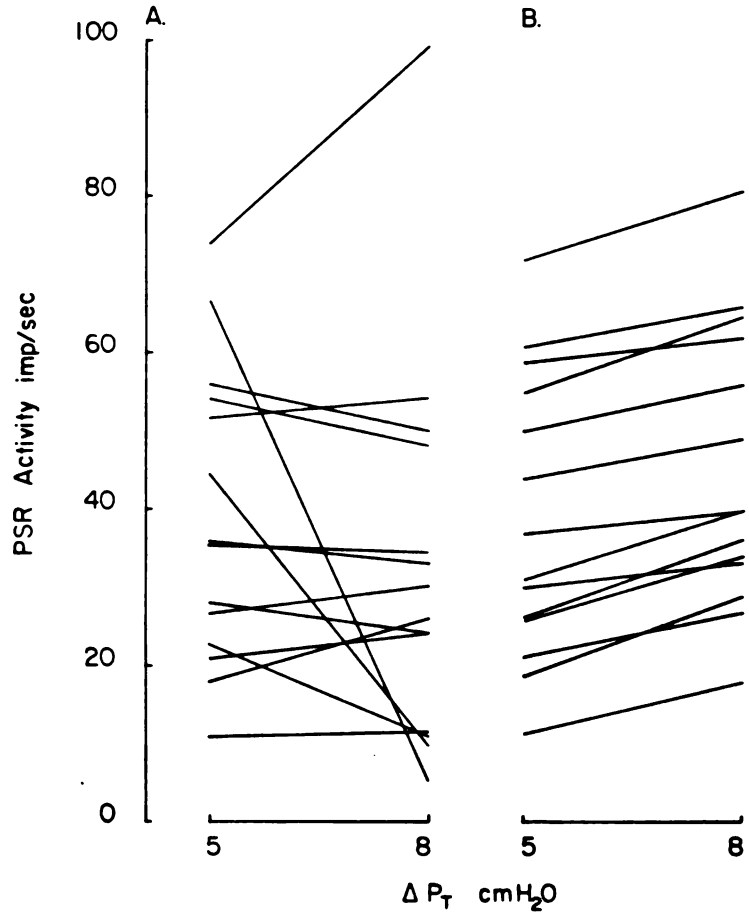

Fig. 3-25. Response of slowly adapting pulmonary stretch receptors (PSRs) in cats to two different modes of stimulation, decreasing C_{DYN} (A) and increasing tidal volume (B). Each regression line represents one PSR response, which was calculated from 6 data points at different tracheal pressure. Note PSR response to decreasing C_{DYN} varied.

and application of NEEP (-2 cm H_2O for 2 ventilator cycles) with a decrease in their activity. The majority of high threshold PSRs became silent. The discharge of low threshold PSRs decreased in both inflation and deflation, and in many firing ceased during deflation. Unlike the response of RARs during removal of PEEP, there was no phase shift in PSR activity. The response of six PSRs in dogs to a long period (2 minutes) of removal of PEEP was similar to that to application of NEEP. When PEEP was removed or NEEP applied for longer periods (one minute or more) PSRs resumed their activity to some extent. This may have been a consequence of the increasing amplitude of the tracheal pressure swings during these maneuvers. Therefore, PSR activity was averaged over the total period. The results are given in Table 3-3.

STUDIES ON C-FIBERS

Effect of Decreasing C_{DYN}

As shown above, decreasing C_{DYN} caused an increase in mean activity of RARs, but had little effect on mean activity of PSRs. In order to determine whether decreasing C_{DYN} had any effect on C-fibers, the mean activity of 6 C-fibers in dogs was examined at two levels of C_{DYN}. When C_{DYN} decreased to about 40% of the maximum value, C-fiber activity increased from 0.6±0.2 to 0.9±0.2 impulses/sec

(Table 3-3). Although this increase was not statistically significant ($P>0.05$), this could have been due to the small sample. However, these results suggest that if decreasing C_{DYN} has any effect on the mean activity of C-fibers, the effect is likely to be small.

Effect of Deflating the Lungs

Six C-fibers in dogs did not respond to either removal of PEEP or application of NEEP (Table 3-3). Their sparse and irregular firing pattern persisted during the experimental procedures.

EFFECT OF VAGAL COOLING ON CONDUCTION IN AFFERENT FIBERS

In 8 dogs the effect of cooling on the impulse activity of 15 RARs were examined and compared with those on PSRs and C-fibers. When vagal temperature was decreased to 10°C, the recorded activity of RARs had decreased on average by approximately 33%, and that of slowly adapting receptors by 75%. At a vagal temperature of 5°C, more than 80% of the total activity of RARs was blocked and about half of the receptors were blocked completely (Fig. 3-26). At the same temperature more than 90% of the total activity of PSRs were blocked, while C-fiber activity underwent no substantial change (Fig. 3-27). C-fibers were not blocked completely until the vagal temperature was reduced to -1°C.

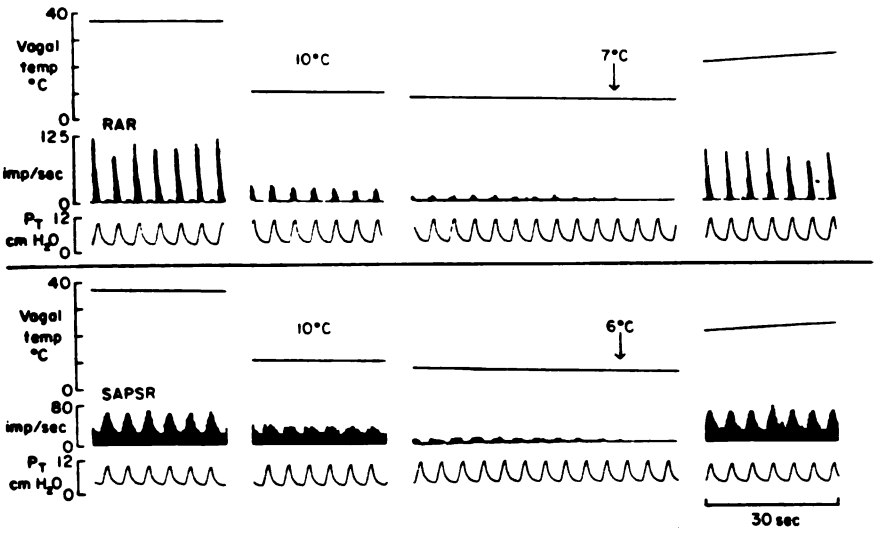

Fig. 3-26. Effect of cooling and rewarming the pulmonary vagus nerves on afferent activity recorded from the ipsilateral cervical vagus nerve; above, a rapidly adapting receptor (RAR); below, a slowly adapting pulmonary stretch receptor (SAPSR). Arrows indicate blocking temperature. Chest open, lungs ventilated artificially. Impulse frequency (imp/sec) recorded by a ratemeter; P_T, tracheal pressure.

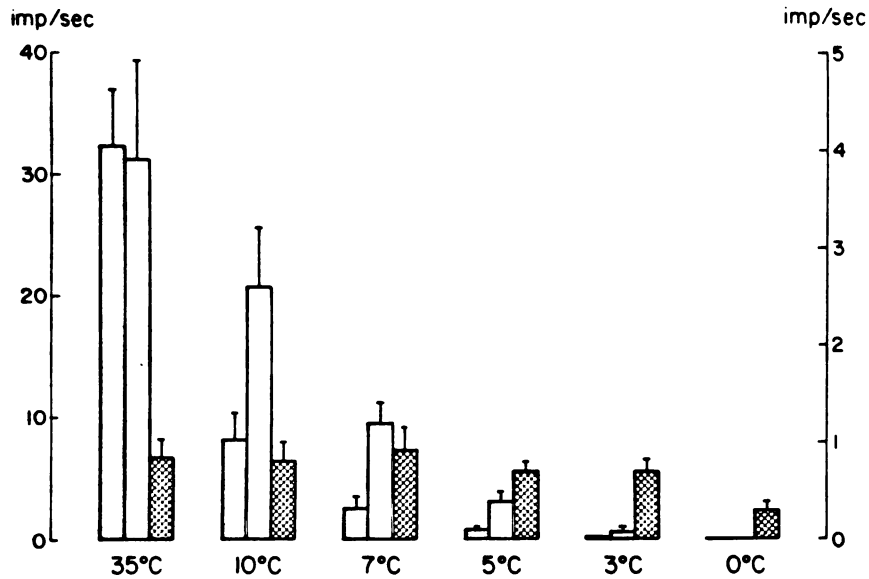

Fig. 3-27. Effect of cooling the vagus nerve on afferent activity in the cervical vagus nerve. Data are means ± SE. Observations on 13 slowly adapting pulmonary stretch receptors (stippled bars; calibration on left), 15 rapidly adapting receptors (open bars; calibration on right), and 14 lung C-fibers (hatched bars; calibration on right). Chest open, lungs artificially ventilated.

REFLEX STUDIES

EFFECT OF RARs ON SECRETION

As described above, RARs are stimulated by three procedures that do not have consistent effects on other pulmonary afferents (Fig. 3-28). These procedures are: 1) decrease in dynamic lung compliance; 2) removal of positive end expiratory pressure from the ventilator outlet; 3) application of negative pressure (-4 cm H_2O) to the ventilator outlet. These three procedures were effective in stimulating RARs in ascending order of magnitude (Table 3-3).

By comparing the effects of these three procedures, it should be possible to separate the influence of RARs on tracheal secretion from that of PSRs and C-fibers. The effect of the three procedures on 6 receptors of each type were examined in dogs (the species to be used in the secretion studies). Results are summarized in Table 3-3. The effects of these procedures on RAR activity in dogs were similar to those in cats and rabbits.

Effects of procedures 1), 2) and 3) on secretion

All three procedures increased submucosal gland secretion.

1) Reduction of C_{DYN}. The rate of submucosal gland secretion was inversely related to C_{DYN}. In 8 experiments (Fig. 3-29) the mean rate of secretion at maximal lung compliance was 3.0±0.3 hillocks/0.6 cm^2/min and this increased to 4.2±0.6 hillocks/0.6 cm^2/min ($P<0.05$) when C_{DYN} was reduced to 63±4.7% of maximum. C_{DYN} was reduced in these experiments by applying NEEP to the ventilator outlet for 60 sec. Since NEEP itself was a powerful stimulus to tracheal secretion, in 5 paired experiments secretion rate was compared at two levels of C_{DYN} after NEEP had been applied. In experiments, to control for the effects of NEEP, NEEP was applied for 60 sec as before, but immediately after the application, the lung was inflated to 3-4 V_T to bring back the compliance to control level. Again, in these 5 paired experiments there was a significant difference ($P<0.05$) in secretion rate at the two levels of C_{DYN} (Fig. 3-30). At control C_{DYN}, the secretion rate was 3.7 hillocks/0.6 cm^2/min and when C_{DYN} was reduced to 68±9% of control, the secretion rate was 5.3±1.4 hillocks/0.6 cm^2/min.

2) Removal of PEEP. Submucosal gland secretion increased proportionately to the degree of deflation of the lungs (Figs. 3-31 and 3-32). The baseline rate of secretion (mean rate of secretion at control) increased from 4.1 ± 0.5 to 7.0±1.2 hillocks/0.6 cm^2/min ($P<0.05$, $n=8$), when PEEP

was removed (Fig. 3-29). The maximum secretion rate also increased significantly from 1.1 to 1.8 hillocks/0.6 cm^2/10 sec ($P<0.05$) when PEEP was removed. The secretion rate always began to increase within the first 10 sec of deflation and usually reached its peak about 20 sec after the onset of deflation (Fig. 3-32).

3) Application of NEEP. Like removal of PEEP, application of NEEP had a similar, but more prominent, effect on secretion rate. The mean and maximum secretion rates increased from 4.1±0.5 to 13.2±1.7 hillocks/0.6 cm^2/min ($P<0.05$, $n=8$) and from 1.1 to 3.8 hillocks/0.6 cm^2/10 sec ($P<0.005$, $n=8$), when NEEP was applied (Fig. 3-29). Similarly, the secretion rate always began to increase within the first 10 sec and usually reached its peak about 20 sec after the onset of application of NEEP (Figs. 3-32, 3-33).

From the above results, the magnitude of the increases in secretion rate appeared to be related to the level of RAR stimulation produced by the different maneuvers (Table 3-3; Fig. 3-29).

Effect on Secretion of Blocking Vagal Reflex Pathways

Blockade of vagal afferents. Selective blockade of myelinated vagal fibers low in the neck abolished the increased secretion induced by the procedures outlined above. The

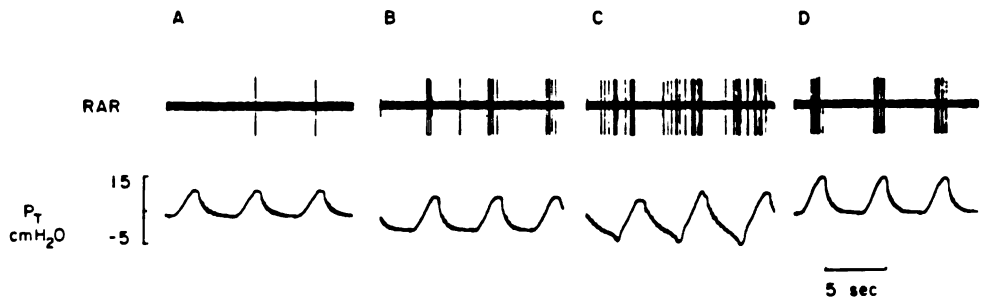

Fig. 3-28. Responses of a rapidly adapting receptor (RAR) in a dog to three different stimuli. A, control; B, removal of positive end expiratory pressure; C, application of a negative pressure (-4 cm H_2O) and D, decreased C_{DYN}. Traces are: RAR action potentials and tracheal pressure (P_T).

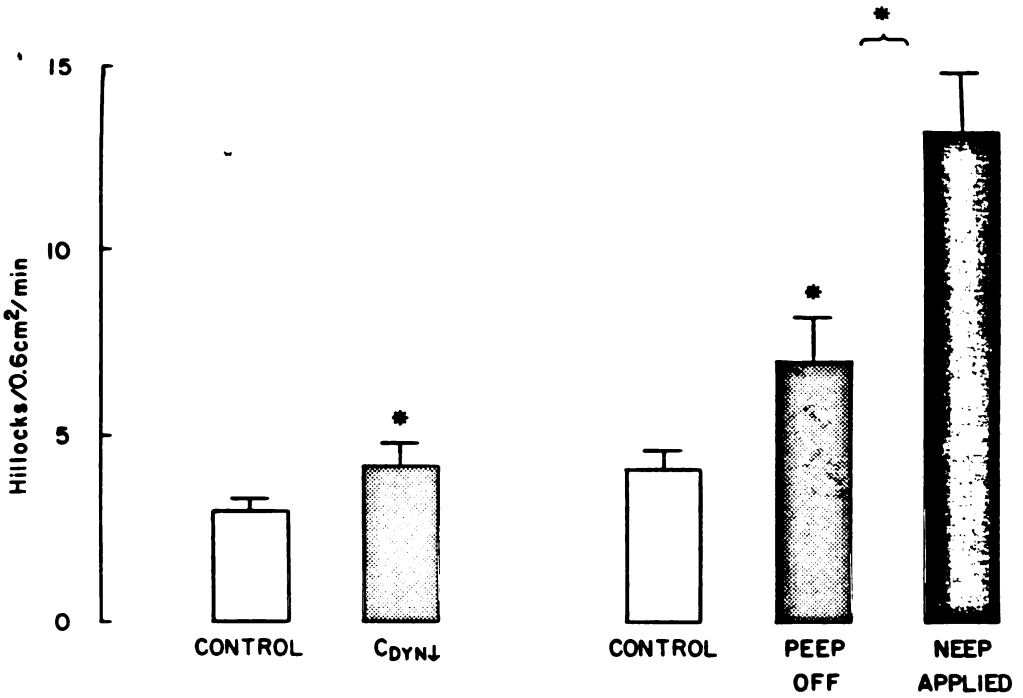

Fig. 3-29. Effects on submucosal gland secretion of three maneuvers known to stimulate RARs, reduction of C_{DYN} (by 37%), removal of positive end expiratory pressure (PEEP OFF) and application of negative end expiratory pressure (NEEP APPLIED). Asterisk denotes significant difference from previous value ($P<0.05$). Note increased secretion rate is directly related to RAR stimulation (Table 3-3). Values are means ± SE.

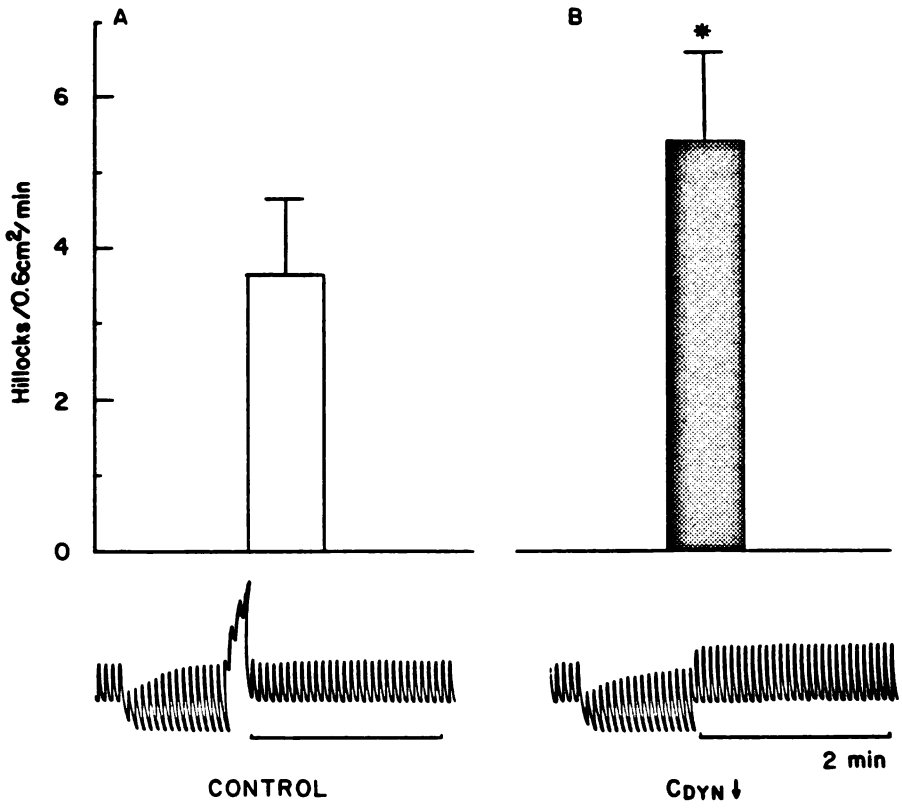

Fig. 3-30. Comparison of secretion rate at high and low lung compliance: In A and B NEEP applied for 1 min (to reduce C_{DYN}). In A, C_{DYN} restored to control by hyperinflation. In B, C_{DYN} reduced on average by 36%. Secretion measured for 2 min (see time bar). Reduction of C_{DYN} caused statistically significant increase in secretion ($P<0.05$) ($n=5$).

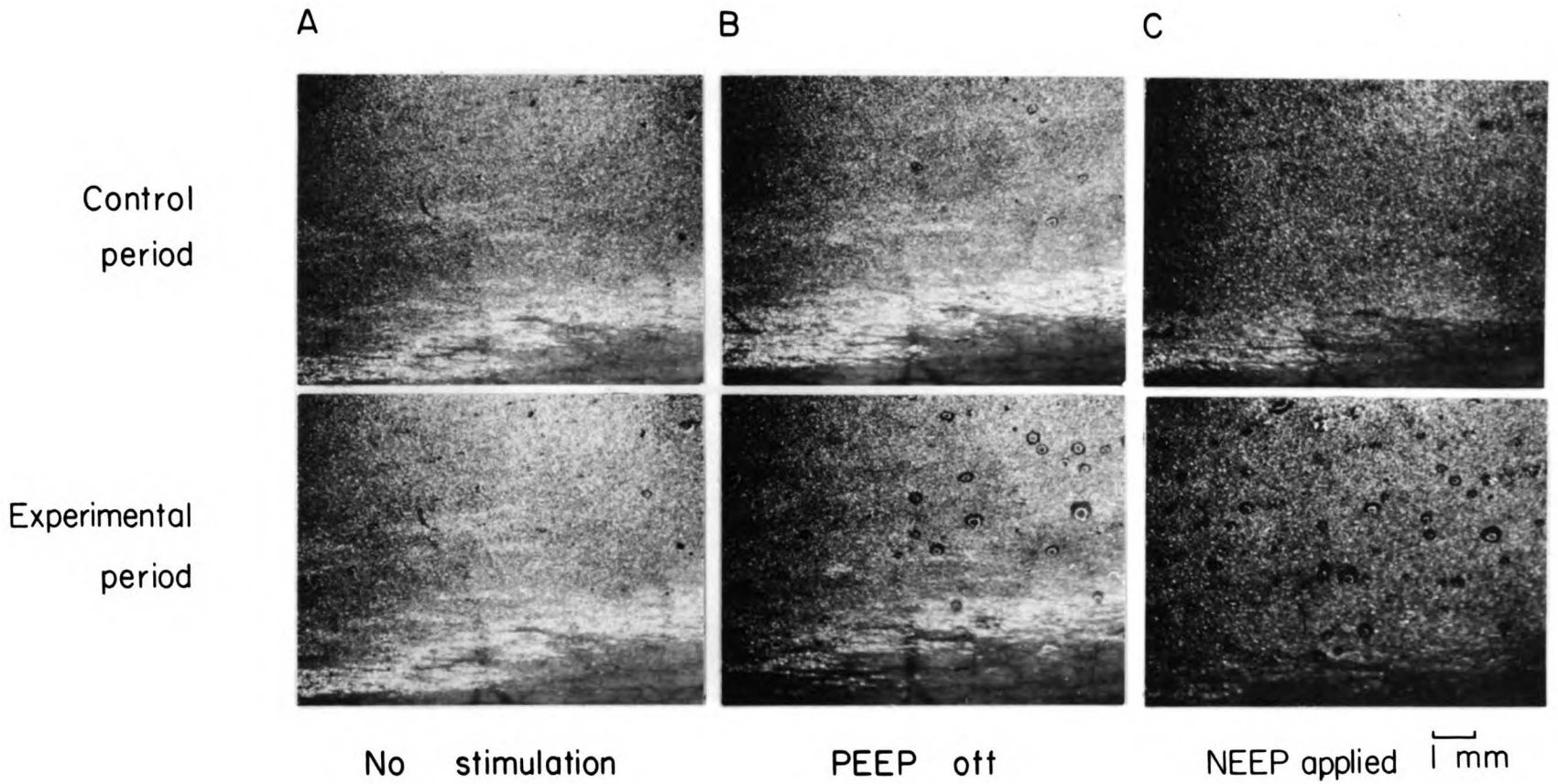
A
B
C
Control
period
Experimental
period
No stimulation
PEEP off
NEEP applied
1 mm

Fig. 3-31. Photomicrographs of tantalum-coated mucosa on lateral wall of upper tracheal segment. A, appearance of mucosa 60 sec (control period) and 120 sec (experimental period) after it had been dried and sprayed with powdered tantalum; B, appearance after 60 sec of control and 60 sec after removal of PEEP; C, appearance after 60 sec of control and 60 sec after application of NEEP.

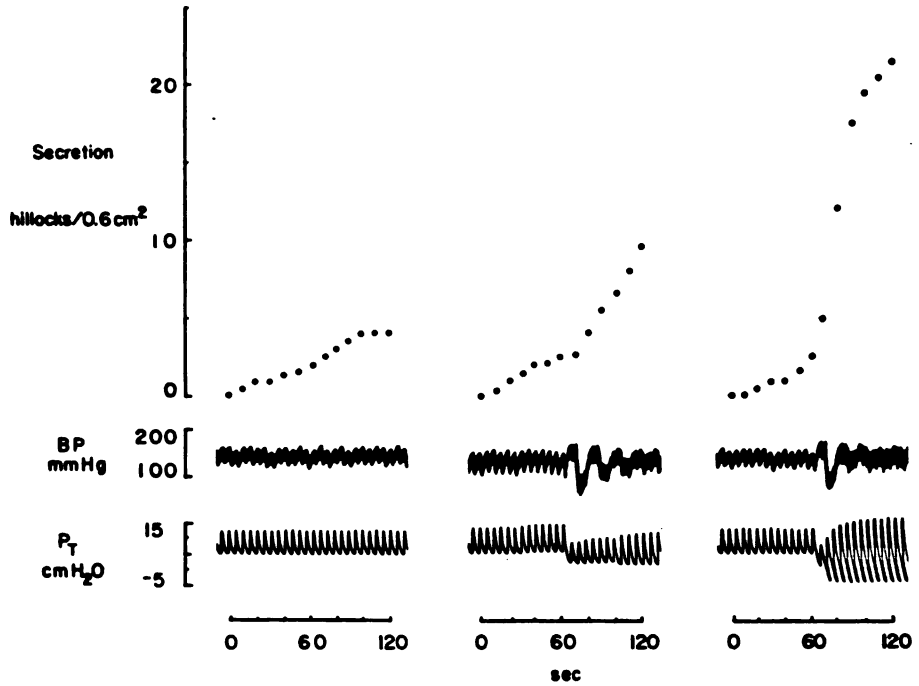

Fig. 3-32. Increased tracheal submucosal gland secretion (hillock formation) caused by experimental maneuvers which are known to stimulate RARs. A, control; B, removal of PEEP; C, application of NEEP. Traces are secretion, arterial blood pressure (BP), and tracheal pressure (P_T).

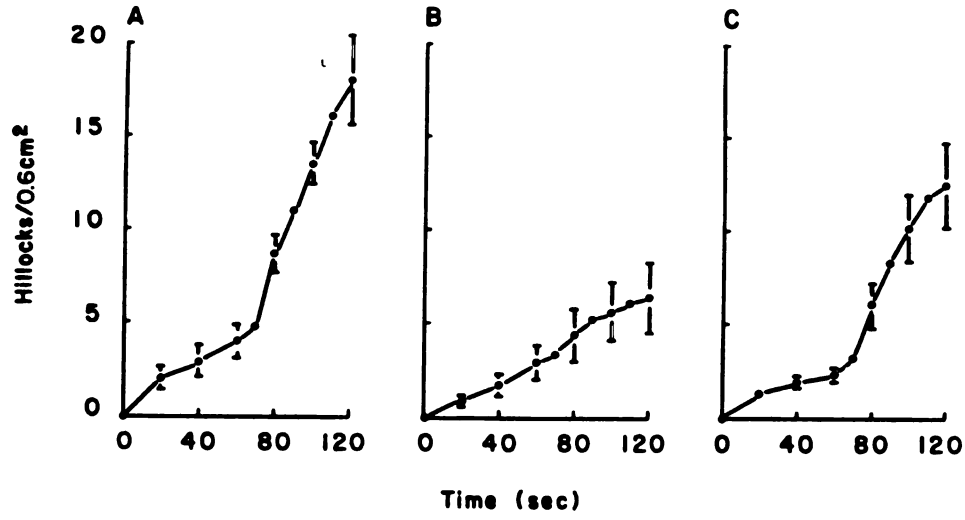

Fig. 3-33. Abolition by vagal cooling of tracheal secretion (0.6 cm^2 field of tracheal mucosa) evoked by application of negative end expiratory pressure (NEEP). NEEP was applied from 60 sec to 120 sec. Temperature of vagus nerves was 37°C (A), 6°C (B) and 35°C (C). Values shown are means ± SE (n=9).

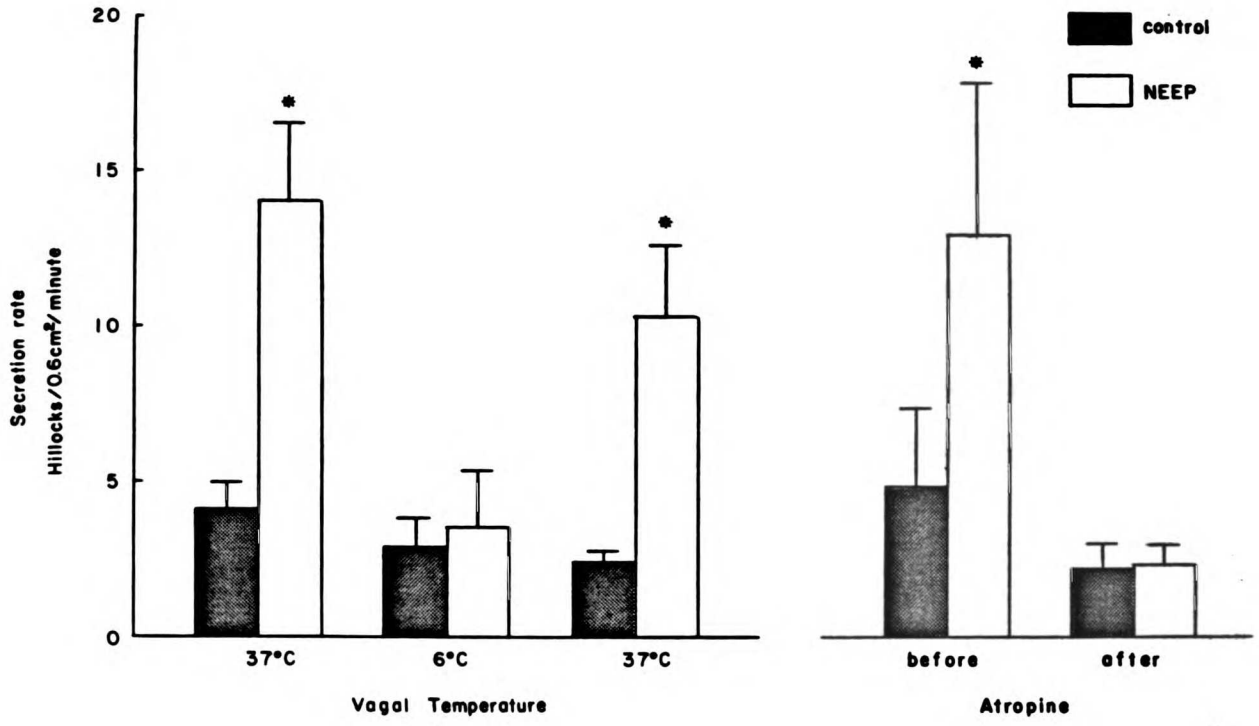

Fig. 3-34. Tracheal submucosal gland secretion evoked by application of NEEP is abolished by vagal cooling to 6°C (n=9) or by administration of atropine (n=4). Asterisk denotes statistical significance ($P<0.05$). Values shown are means ± SE.

	HR (beats/min)	BP (mmHg)	pH	PCO_2 (mmHg)	PO_2 (mmHg)
Control	182±10	129±11	7.42±0.01	32.1±2.8	166±13
PEEP	168±11*	137±10*	7.42±0.01	32.3±2.6	165±15
Control	189±8	128±11	7.41±0.02	37.6±1.3	192±11
NEEP	163±12*	143±11*	7.41±0.02	38.5±1.3	158±11*

Table 3-7. Effects of removing positive end expiratory pressure (PEEP; n=8) and applying negative end expiratory pressure (NEEP; n=7) on cardiovascular variables, arterial blood gases and pH in the dog. Heart rate (HR) arterial blood pressure (BP) and arterial blood pH, PCO_2 and PO_2 were measured after PEEP had been removed or NEEP had been applied for 2 minutes. Values are means±SE. Asterisk denotes statistical significance ($P<0.05$) from control value.

increase in secretion caused by application of NEEP was blocked by cooling the vagus nerves to 6°C (n=9), and the response was restored by rewarming the nerves (Figs. 3-33 and 3-34). The secretory response to application of NEEP was also abolished by bilateral cervical vagotomy. During vagal cooling or after vagotomy, stroking the laryngeal mucosa with a cotton-tipped applicator, which is known to be a powerful stimulus to tracheal submucosal gland secretion (Phipps and Richardson, 1976; Davis et al, 1982 a), invariably caused a large increase in secretion, indicating that the motor pathway was intact.

Blockade of vagal efferents. The secretory response to application of NEEP was also abolished by intravenous injection of atropine (n=4) (Fig. 3-34). The response to stroking the laryngeal mucosa disappeared after atropine. Furthermore, the baseline rate of secretion was almost halved after either atropine or cervical vagotomy (n=3) ($P<0.05$).

Cardiovascular Variables and Blood Gases

During removal of PEEP or application of NEEP, there were small but significant ($P>0.05$) changes in arterial blood pressure and heart rate. The mean arterial blood pressure increased and heart rate decreased. These hemodynamic effects seemed also positively related to the degree of

deflation (Table 3-7). Arterial blood pH and blood gases, sampled at the end of each experimental procedure seemed not to be significantly affected by the deflation except that Pa_{O_2} decreased ($P<0.05$). However, during deflation Pa_{O_2} was still far above the normal oxygen tension in arterial blood because the lungs were ventilated with a high oxygen mixture. The results of blood gases are summarized in (Table 3-7).

EFFECT OF VAGAL COOLING ON BREATHING

In 7 spontaneously breathing rabbits, the blocking temperature of the Hering-Breuer inspiration inhibitory reflex was first determined and then the effect of vagal cooling on the pattern of breathing was examined. When the vagal temperature was 37°C, hyperinflating the lungs (FRC + 2 V_T) invariably evoked a period of inspiratory inhibition which was terminated eventually by a vigorous inspiratory effort. Cooling the cervical vagus nerves to 10°C abolished the reflex inhibition in 4 rabbits and reduced the reflex effect by more than 90% in the remaining 3.

Inspiratory time (Ti) and expiratory time (Te) were measured as the vagus nerves were cooled to assess the effects of different vagal afferents on breathing. Ti increased when the vagus nerves were cooled from 37°C to 15°C, and

the Hering-Breuer reflex was blocked by cooling the vagus nerves from 15°C to 10°C. At 10°C the blockade of the Hering-Breuer inflation-inhibitory reflex was assumed to be complete, because further cooling of the vagus nerves below 10°C had no additional significant influence on Ti (Fig. 3-35). However, Te underwent no substantial change until temperature decreased below 15°C. Then at each cooling step Te increased gradually and significantly until the vagus was cooled to 0°C ($P<0.05$; Fig. 3-35).

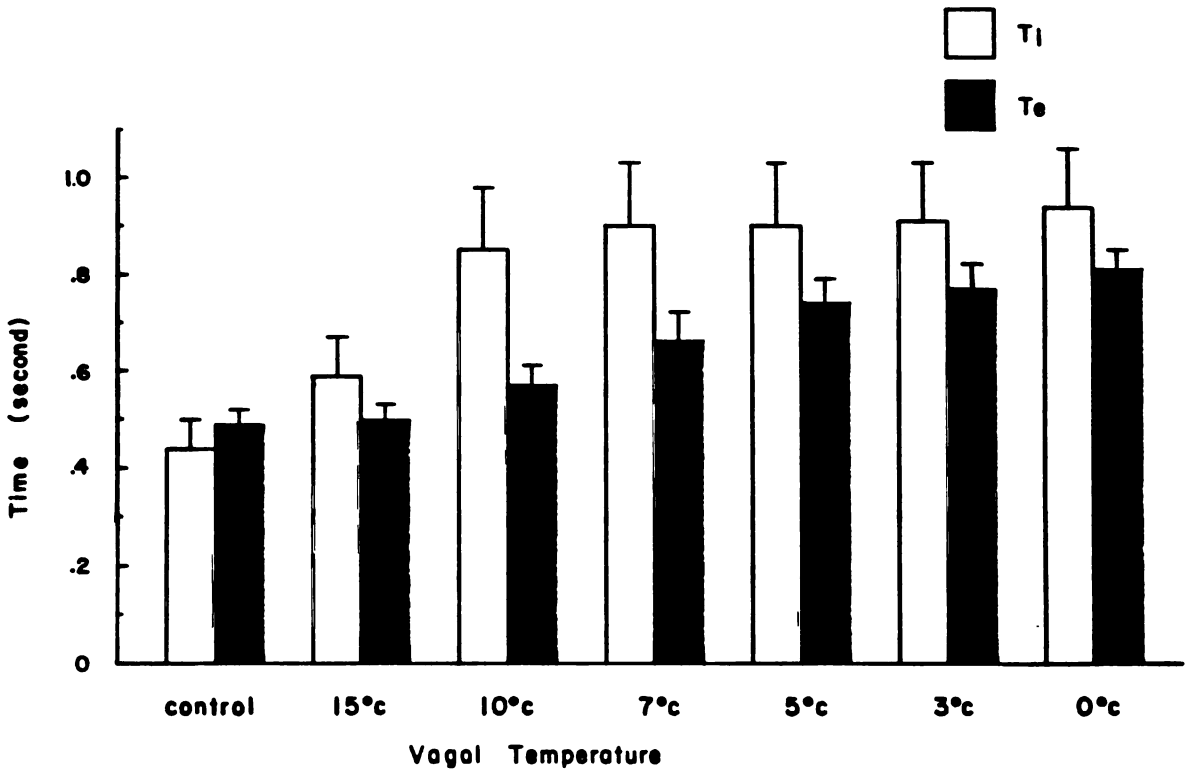

Fig. 3-35. Effects of cervical vagal cooling on inspiratory time (Ti) and expiratory time (Te) in rabbits (n=7). Note, Ti increased initially and underwent no change after vagal temperature reduced below 10°C. Te gradually increased at each step of cooling below 15°C.

DISCUSSION

AFFERENT PROPERTIES OF RARs

CONTROL DISCHARGE OF RARs

The afferent characteristics of the rapidly adapting receptors (RARs) examined in the present study were generally similar to those of the RARs previously described in cats (Knowlton and Larrabee, 1946; Armstrong and Luck, 1974), rabbits (Mills et al., 1969; Sellick and Widdicombe, 1969), dogs (Sampson and Vidruk, 1975; Pisarri et al., 1986; Jonzon et al., 1986) and guinea pigs (Bergren and Sampson, 1982). In all 4 species, impulse activity varied widely under control conditions, with most receptors firing irregularly and at low frequencies, so that the average input is low. In the present study the basal activity of RARs was sparse and irregular with an average frequency of about 1 impulse/sec. However, even this could be an overestimate of the actual RAR activity, because some less active or inactive RARs may have been missed during the seach for the receptors. The only high basal activity of RARs was observed in rabbits by Sellick and Widdicombe (1970), who reported an average firing rate of 16.9 impulses/sec. Such extremely high activity,

which has never been described in other studies, is closer to the peak frequency observed in the present experiments.

In the present experiments the control activity of some RARs had an obvious cardiac modulation, which in some receptors occured during deflation (Fig. 3-3) and in others during inflation (Fig. 3-4). The cardiac modulation might depend on the closeness of the receptor to the heart, being more prominent in receptors close to the heart and increasing during inflation, because of a more direct contact of the heart with the receptor field. In such cases, simply displacing the heart by lifting the overlying pericardium was sufficent to abolish the cardiac activity. My general impression was that receptors far away from the heart had little or no cardiac modulation during inflation. It is possible that during lung inflation, any cardiac modulation of these more distant receptors was masked by the buffering action of the inflated lungs. Certainly the cardiac modulation became more prominent during the deflation phase (especially when PEEP was removed) or when the lungs were kept deflated, as shown in Fig. 3-17.

The fact that RAR activity often had a cardiac modulation when the lungs were deflated at constant pressure (0 to 3 cm H_2O) might explain the relative absence of adaptation during deflation, compared with the marked adaptation that

occurs during constant pressure inflation. Knowlton and Larrabee (1946) drew attention to the relative absence of adaptation when activity was induced by deflating the lungs, but did not comment on whether it is due to the persisting cardiac rhythm, although this appears to be so from their illustration of this phenomenon (Knowlton and Larrabee, 1946, Fig. 2). Hence the unadapted cardiac activity, as illustrated in Fig. 3-17 of the present results, could greatly increase the basal activity during deflation, and greatly reduce the adaptation index for this particular stimulus.

Since the mechanical changes affecting the receptor during each respiratory and cardiac cycle determine the firing pattern, it is not surprising that many different RAR firing patterns have been described in the literature (see INTRODUCTION). These different patterns could be explained by differences in the magnitude of the respiratory and cardiac modulation under different experimental conditions. For example, at low dynamic lung compliance (C_{DYN}), high V_T or high PEEP, we expect to see a clearer respiratory modulation; however, at high C_{DYN}, low V_T or low PEEP, we expect to see a clearer cardiac modulation.

EFFECT OF DECREASED C_{DYN} ON RAR ACTIVITY

Up to now, the opinion has been widely held that most RARs in healthy lungs are either silent or have only a sparse discharge during normal ventilation, becoming active only when inflation volume or inflation rate increase, or when the receptors are stimulated experimentally by a variety of physiological or pharmacological interventions (see INTRODUCTION). The present results and those of Jonzon et al (1986) challenge this assumption, and suggest, on the contrary, that a vigorous phasic discharge may be evoked in healthy lungs by decreases in lung compliance within the physiological range.

The present results provide quantitative evidence that RAR activity is inversely related to C_{DYN} over the physiological range. They also demonstrate that as compliance decreases the pattern of firing becomes more uniform, the receptors now discharging with a high frequency at the peak of inflation. The response to each stepwise decrease in C_{DYN} adapted significantly with a half life around 20 sec. After adaptation, RAR activity reached a steady state that was also inversely related to C_{DYN}. This steady state increase in RAR activity, rather than the immediate increase, probably corresponds to the increase in activity likely to occur when compliance decreases naturally.

The values for maximal compliance observed under the conditions of the present experiments were similar to those reported previously in rabbits and cats (Crosfill and Widdicombe, 1961). Neither lung compliance nor receptor activity was altered in the longer term by the experimental procedures, and both reverted to their initial level when the lungs were hyperinflated. Decreases in lung compliance comparable to those in the present experiments have been observed in healthy lungs during quiet breathing in dogs (Mead and Collier, 1959) and human subjects (Ferris and Pollard, 1960). In both these earlier studies, large inflations approaching vital capacity were used to obtain maximal compliance, and in human subjects lung compliance before hyperinflation was often 20% below this maximum. Thereafter, during quiet breathing, compliance decreased spontaneously, falling by 50% over a 2 hour period in dogs (Mead and Collier, 1959) and by 26-40% over a 30 minute period in humans (Ferris and Pollard, 1960). Hence the range of compliance over which RAR were examined in the present experiments probably included levels above and below those likely to prevail in healthy lungs during quiet breathing.

Before considering further the mechanism by which a decrease in C_{DYN} stimulates RARs it is necessary to discuss some of the factors known to affect RAR activity.

MECHANISM OF STIMULATION OF RARs

The question of the precise mechanism of stimulation of RARs is still unsolved. Pulmonary RARs have been thought to sense inflation volume, airway flow rate, tracheal pressure, rate of change of tracheal pressure (dp/dt) and dynamic lung compliance (see INTRODUCTION: RESPONSE TO MECHANICAL CHANGES). Since these variables are related, alteration of one may result in changes in the others. Moreover, all these variables represent gross mechanical changes in the respiratory system; none of them tells what the specific stimulus to a given RAR is. But whatever the mechanism, the final effect of an increase in RAR firing must be the result of distortion of the receptor sensory structure. Hence the exact mechanism of stimulation will not be clear until more is known about the morphology of the receptor terminals and their relation to the various structural elements in the airway wall. The present interest is to consider which of these factors is the major determinant of RAR activity.

Rapidly adapting mechanoreceptors co-exist with slowly adapting mechanoreceptors in many organs and tissues, and research has been conducted on their similarities and differences. (Davis, 1961; Catton, 1970; Burgess and Perl, 1973). Generally speaking, slowly adapting receptors have a low

threshold, and sense a sustained change (stimulus); rapidly adapting receptors have a higher threshold and sense mainly the rate of the change applied to the receptors, i.e. the first derivative of the change; the most rapidly adapting receptors, also have a response component related to the second derivative of the change.

The firing behavior of RARs in the lower respiratory tract has some features in common with that of rapidly adapting mechanoreceptors in other locations. Firstly, they have a rapid adaptation rate with little and irregular activity during a sustained stimulus (see INTRODUCTION and present results). Secondly, they have an off-stimulation response (Knowlton and Larrabee, 1946). Widdicombe (1954 b) also observed this phenomenon in tracheal RARs but not in pulmonary RARs. Thirdly, they are reported to have a dynamic sensitivity to the rate of airflow (Sullivan and Read, 1975; Pack and DeLaney, 1983) and tracheal pressure (Jonzon et al, 1986; present results). Therefore, it seems reasonable to conclude that RARs mainly sense the first derivative of the stimulus. Now the question is which of the several factors mentioned earlier in this section is the most effective stimulus.

Pack and DeLaney (1983) agreed with Sullivan and Read's proposal (1975) that RARs sense the rate of airflow, because

they observed a positive relationship between RAR activity and inspiratory flow rate. However, as Pack and Delaney mentioned, the sensitivity of RARs to flow rate also depends on lung volume, so that the larger the lung volume, the more active the receptors at a given flow rate. In their experiments, the effects of different flow rates were examined with a fixed inflation volume. With this method, dp/dt should increase with an increase in flow rate. Moreover, as lung volume increases a point is eventually reached at which compliance decreases, so that dp/dt tends to increase even though flow rate is kept constant. Hence the increase in RAR activity might be better explained by the increase in dp/dt than by the increase in flow rate. The idea that dp/dt is a more accurate description of the stimulus than flow rate is supported by the following evidence.

Firstly, receptor activity correlates better with transpulmonary pressure than with lung volume (Widdicombe, 1954 b; Sant'Ambrogio, 1982).

Secondly, a linear relation between RAR activity and lung stiffness, and hence between RAR activity and dp/dt has been shown in dogs (Jonzon et al, 1986), cats and rabbits (present results). In these experiments, V_T and inspiratory time were held constant so that flow rate was also constant. Therefore, any change in tracheal pressure must have been

accompanied by a proportional change in dp/dt. Because lung stiffness is directly proportional to the change in tracheal pressure, it is also proportional to dp/dt. Therefore, the relationship between RAR activity and dp/dt was also linear (Fig. 4-1).

Thirdly, Widdicombe (1954 b) stimulated RARs by distending the trachea and bronchi indicating that the receptors can be stimulated by increasing pressure without an increase in flow, since by that maneuver only distending pressure was exerted on the receptors and no shearing force was applied.

Fourthly, Sellick and Widdicombe (1970) observed an increase in RAR activity after deflation of the lungs in rabbits that were breathing spontanously. This could be explained by an increase in dp/dt, because transpulmonary pressure, V_T and respiratory frequency increased. These three factors acting together will undoubtedly increase dp/dt. Sellick and Widdicombe also observed that after hyperinflation of the lungs, RAR activity decreased in spite of an increase in V_T and respiratory rate and hence an increase in airflow. Hence the sensitivity of RARs to airflow, if any, must be very low. At this point, it is safe to conclude that the rate of airflow, at most, is an unimportant stimulus to RARs. Whereas there are good grounds for believing

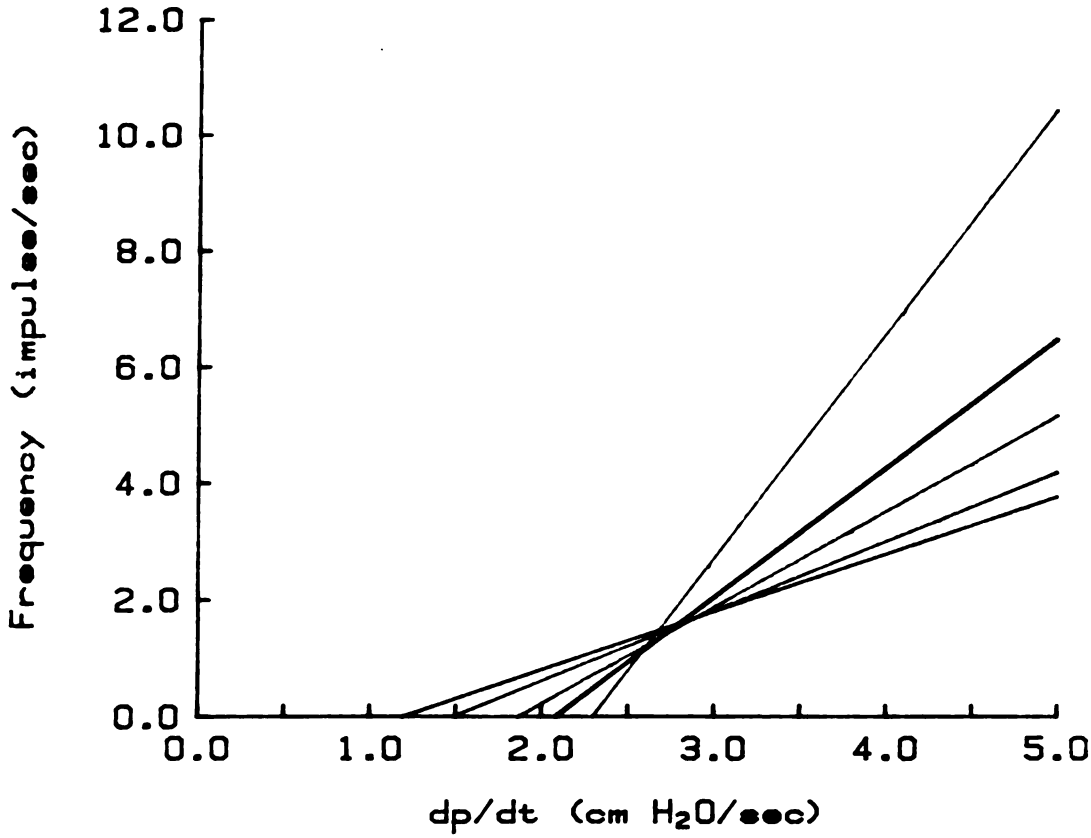

Fig. 4-1. Relationship between firing frequency of rapidly adapting receptors and the rate of change of tracheal pressure (dp/dt) in cats. Each line represents a different period of time after mechanical maneuvers. The regression lines from top down are at 10, 30, 50, 70 and 90 sec respectively. The data presented in this figure are the same data presented in Fig. 3-8.

that dp/dt is an important component of the stimulus to RARs.

Nevertheless, the sensitivity of RARs to transpulmonary pressure and dp/dt cannot completely explain the stimulation of RARs. Firstly, RAR activity did not show an instantanous correlation with dp/dt (present results). Secondly, it is also clear that increasing lung stiffness increases RAR discharge with a component which is independent of dp/dt (Jonzon et al, 1986). Thus, it is important to separate the factors of transpulmonary pressure and dp/dt from lung stiffness. The crucial experiments were those in which the receptor response to a given increase in transpulmonary pressure and dp/dt produced by simply increasing the ventilator stroke volume was compared with the response to an equivalent increase in airway pressure and dp/dt obtained by increasing lung stiffness.

If dp/dt was the most prominent determinant of RAR activity, then these two modes of stimulation should have evoked similar increases in the activity of RARs; once again, if airflow rate was an effective stimulus, then an increase in flow rate by increasing V_T should elicit a higher activity of RARs. However, it is clear that lung stiffness was a more powerful stimulus in the present experiments (see RESULTS); and it is concluded that of the factors

mentioned lung stiffness is the major determinant of RAR activity. Support for this was provided by the observation that when RAR activity was plotted as a function of lung stiffness, the slope of the relationship did not differ significantly for either mode of stimulation.

The present results do not suggest that changes in airflow resistance play a prominent part in stimulating RARs. Theoretically, the method of increasing lung stiffness by periodic removal of PEEP could have had two-fold mechanical effects on the lung: 1) an increase in parenchymal elastance induced by collapse of terminal bronchioles or alveoli, and progressive disappearance of surfactant from the terminal airways when the lungs were allowed to deflate. Hyperinflation would restore parenchymal elastance to its original level by reopening the small airways and alveoli and by promoting the reappearance of surfactant in the surface film (Nicholas et al., 1982). 2) a vagal reflex increase in smooth muscle tone, and hence an increase in airflow resistance, evoked by periodic reduction of lung volume. Because RARs are located in the more central airways, upstream to the principal site of airflow resistance (Sant'Ambrogio, 1982), both components could contribute to the increase in receptor discharge.

However administration of atropine had no obvious

effect on maximal C_{DYN} or on the stepwise reductions in C_{DYN} produced by removing PEEP, and it had only minor effects, if any, on receptor sensitivity to increasing lung stiffness. This is in contrast to the prominent effects of changes in bronchial smooth muscle tone on PSR activity, which cause a respiratory modulation of discharge even when the lungs are motionless (Richardson et al, 1984). Therefore, it is concluded that stimulation of RARs in the present experiments was largely a consequence of increased parenchymal elastance, and that neurally induced changes in smooth muscle tone, if any, were relatively unimportant.

Since removal of PEEP and application of NEEP are powerful stimuli to RARs, it could be argued that the increase in RAR activity evoked by increasing lung stiffness by periodically removing and then replacing PEEP is essentially due to the residual effect of lung deflation, because with each step of deflation the strength of stimulation increased. Therefore the adaptation of RAR activity could be simply due to the withdrawal of stimulation. However, the results disprove this argument. First, after C_{DYN} was reduced RAR activity does not adapt completely to the control level, but partially adapts to reach a steady state above control. Second, static inflation of the lungs also has a greater effect on the RAR activity at high lung stiffness than at control. Third, after restoration of PEEP, the discharge

pattern of RARs shifted from bursts in deflation to bursts in inflation. So it is safe to conclude that RAR activity is positively related to lung stiffness, and is not simply the prolonged consequence of deflation alone.

Experimental results have shown that PSRs actually sense the tension of airway walls (Roumy and Leitner, 1976). I speculate that like PSRs, RARs also sense tension. But unlike PSRs, they mainly sense the rate of change of tension (dT/dt).

I, therefore, further speculate that airway pressure mainly reflects the forces operating in a circumferential direction on the airway walls, increasing circumferential tension (Sant'Ambrogio, 1982; Roumy and Leitner, 1976). Increasing lung stiffness, however, may 'tether' the airways in an axial direction, and produce an additional, longitudinal distortion of the receptor. Tracheal RARs are thought to have receptive fields that spread axially (Fisher, 1964; Samt'Ambrogio et al, 1978). If the sensory arborisations of RARs in bronchi are also oriented in an axial direction, this would explain why increased parenchymal elastance has such a marked effect on RAR discharge.

If dT/dt is the major determinant of RAR activity, then the increased longitudinal stretch of the airway walls

as lung stiffness increases may act to increase the sensitivity of RARs to transpulmonary pressure and dp/dt. This hypothesis could explain the properties of RARs observed in the present studies as follows.

The rapid increase in RAR activity at the onset of a square wave increase in transpulmonary pressure is probably due to a sudden increase in dynamic tension. During the period of sustained inflation, although tension remains high, the dynamic component disappears, and RAR activity adapts. When lung stiffness increases, RARs are sensitized to transpulmonary pressure and dp/dt and application of a similar square wave of transpulmonary pressure results in an increase in both the dynamic and adapted response of the receptor.

Tension is more linearly related to pressure than to volume. That might be why RAR activity was more linearly related to $1/C_{DYN}$ than to C_{DYN} in the present experiments.

REFLEX SIGNIFICANCE OF DECREASED C_{DYN}

Although the reflex influence of RARs has been thought previously to be important only during abnormal lung conditions, such as lung congestion and microembolism (Widdicombe, 1974), the present results suggest that the receptors may

have significant effects during quiet breathing. RARs are known to evoke gasps or sighs when stimulated acutely by large, abrupt inflations and deflations of the lungs (Larrabee and Knowlton, 1946; Davies and Roumy, 1982), and attention has already been drawn to the significance of this 'gasp reflex' as a mechanism for reversing alveolar collapse (Reynolds, 1962; Sellick and Widdicombe, 1970). For example, the incidence of spontaneous gasps or sighs in anesthetized cats has been found to increase as lung compliance decreases (Reynolds, 1962). Moreover, it is conceivable that the excitatory effect of RARs on inspiratory motor output can also be exerted in a 'breath-by-breath' fashion. RARs are thought to cause reflex bronchoconstriction (Mills et al, 1969; Sellick and Widdicombe, 1969). The combined effect of increased inspiratory drive and an increased bronchomotor tone that stabilizes dead space will be to maintain tidal volume and alveolar ventilation as the lungs become stiffer. Hence pulmonary RARs may have an important physiological role in providing the respiratory centers with information regarding any increase in the force required to expand the lung, and under conditions of increased lung stiffness their positive feedback influence on inspiratory motor output could acquire a true homeostatic significance.

EFFECTS OF DECREASED C_{DYN} ON PSR ACTIVITY

Although the principal reason for embarking on the present study was to investigate possibilities of a physiologic, rather than a pathologic role for RARs in the control of respiratory events, a secondary reason was to attempt to define a selective stimulus to RARs, so that their reflex properties could be examined more satisfactorily. Having determined that RARs were highly sensitive to changes in compliance, I then proceeded to determine whether PSRs were equally sensitive, and to examine the response of PSRs to other procedures, such as removal of PEEP and application of NEEP.

PSRs, like RARs, are mechanoreceptors, and share many properties with RARs (Sant'Ambrogio, 1982). It is certainly interesting to compare the response of PSRs to decreased C_{DYN} with that of RARs. Since Adrian (1933) demonstrated that PSR activity was related to lung volume, other investigators (Knowlton and Larrabee, 1946; Widdicombe, 1961) have shown that lung volume is not the only factor which influences PSR discharge, because a fixed inflation volume becomes less effective in stimulating PSRs after lung compliance has increased. Therefore, some authors (Widdicombe, 1961; Sant'Ambrogio, 1982) considered that decreasing lung compliance was also a physiological stimulus to PSRs. However, as

stated above a decrease in lung compliance is always accompanied by an increase in peak tracheal pressure. Therefore, it is possible that any increase in PSR activity when C_{DYN} decreased is due to the increase of tracheal pressure.

Actually, the present results showed that PSRs responded to decreases of C_{DYN} inconsistently, an inconsistency that has also been reported by Widdicombe (1961). If a decrease in C_{DYN} were an important stimulus to PSRs, PSR responses should have been more like those of RARs and mean activity and peak activity would have increased when C_{DYN} decreased.

Theoretically, the maneuver used to decrease C_{DYN} could have collapsed some lung units and induced an uneven distribution of air in the lungs (Anthonisen, 1963). Activity in PSRs supplying collapsed lung units would tend to decrease, whereas activity in PSRs supplying uncollapsed lung units would tend to increase. Thus, uneven distribution of air would complicate the situation and make it difficult to assess the relative effectiveness of the two modes of stimulation - decreasing C_{DYN} and increasing tracheal pressure.

We can assume that few lung units collapsed completely, because only 3 of 81 PSRs ceased firing after C_{DYN} was decreased. However, when a lung unit is partially collapsed, the pressure threshold of the PSRs supplying that unit

is likely to increase. A comparison of the response of PSRs to a reduction of C_{DYN} and to an increase of V_T revealed a further difference between RARs and PSRs. When the responses are compared at the same transpulmonary pressure and dp/dt, it was clear that in the case of PSRs an increase in V_T was a more effective and consistent stimulus than a decrease in C_{DYN}. In general the activity at peak tracheal pressure did not differ markedly for the two modes of stimulation, but the lack of effect of a reduction in C_{DYN} on mean firing frequency of PSRs was largely due to the fact that activity in deflation was markedly decreased as the lungs became stiffer. This is probably because after partial collapse the lung units have a longer time constant for expansion, so that the PSRs will discharge over a shorter period of the cycle. Once the lung units expand, however, peak inflation pressure will be the same for all, and by the same token, all PSRs will be subjected to the same distorting force at the peak of inflation.

Presumably, those PSRs which were stimulated by decreased C_{DYN} were located upstream to the collapsed lung units and would sense the gross change in tracheal pressure. Thus, the similar responses of those PSRs to the two different modes of stimulation (see RESULTS) suggests that the increase in PSR activity when C_{DYN} was decreased was due to the concomitant increase of tracheal pressure.

By comparing the RAR and PSR responses to the two modes of stimulation, it can be concluded that the two mechanoreceptors sense different mechanical stimuli, RARs are more responsive to an increase in lung stiffness while PSRs are more responsive to an increase in volume or pressure.

Removal of PEEP and application of NEEP had opposite effects on PSRs and RARs. Thus although both manuevers were very effective stimuli to RARs they usually reduced the activity of PSRs.

HISTAMINE EFFECTS

In most previous studies (Mills et al, 1969; Armstrong and Luck, 1974; Sampson and Vidruk, 1975), histamine was injected into the right atrium, as in the present experiment, but I have not found any account of the time of onset of RAR activity in response to histamine, nor of the time taken to produce a maximal increase in firing, and there has been little attempt to correlate temporally the RAR activity with mechanical changes in the lungs. If RARs were stimulated as a direct action of the chemical, their firing pattern in response to a bolus injection of histamine would be likely to resemble the C-fiber firing pattern evoked by chemical stimulation, with the greatest activity

at the onset, and an irregular discharge that returns to control as the chemical is washed away (Figs. 3-19 and 4-2).

The results obtained with the present experimental design do not allow me to form any definite conclusions about the mechanism of histamine effects. In cats the onset of activity after histamine injection occurred with a latency of about 10 sec, and coincided with the increase in tracheal pressure. The response at this point was similar to that obtained when lung stiffness was increased by removing and then replacing PEEP, and it had a clear respiratory modulation. In rabbits the onset of activity occured some sec before the increase in tracheal pressure, the respiratory modulation was not so clear, and changes in lung mechanics could not fully account for the initial response. In both cats and rabbits the maxmal response of RARs was relatively late, and did not occur until approximately 20 sec after injection, which seems somewhat surprising if the response is simply explained by a direct chemical effect and a change of lung mechanics. However in both cats and rabbits there was a clear cardiac modulation of the late response, which is consistent with the possibility that the increase in pulse pressure and cardiac activity produced by histamine played a significant part in the response.

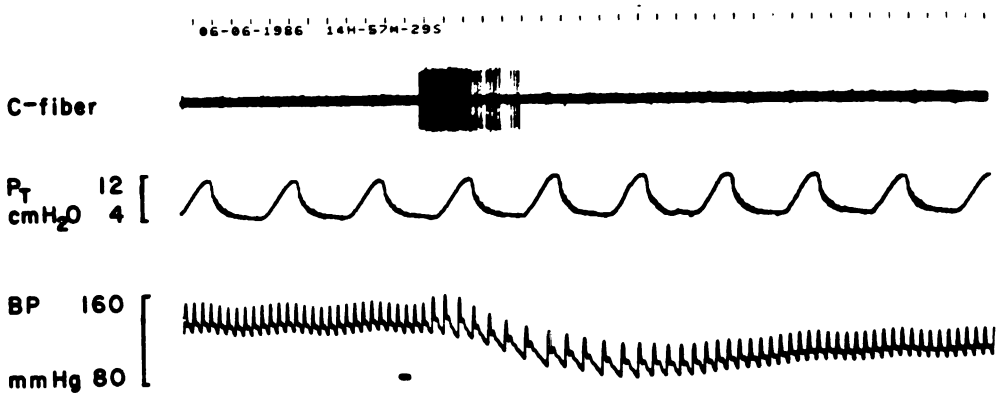

Fig. 4-2. The response of a pulmonary C-fiber to the right atrial injection of capscaicine (20 μg/kg) in a dog. The traces are C-fiber action potentials; tracheal pressure (P_T); arterial blood pressure (BP). On the top the interval beween two small dots are one sec. At the bottom the black bar is the marker for injection. Note the C-fiber responds to capscaicine with a very short latency and very high initial discharges.

EXAMINATION OF REFLEX PROPERTIES OF RARs

POSSIBLE INFLUENCE ON BREATHING

The present results in urethan-anesthetized rabbits confirm the hypothesis that a pulmonary afferent input distinct from the volume-related input responsible for Hering-Breuer reflex causes an increase in breathing frequency. Thus when the vagus nerves were cooled progressively the Hering-Breuer reflex was abolished at about 10°C; further cooling the nerves produced a progressive increase in Te, which suggests that the reflex influence of RARs might shorten Te. These results agree with previouse reports (Fishman et al, 1973; Davies et al, 1978). However, my intepretation of the results is different, because afferent C-fibers from the lungs are also thught to shorten Te (Miserocchi et al, 1978; Coleridge and Coleridge, 1984; Pisarri et al, 1986). An input from C-fibers which shortens Te is also suggested by the present results.

Two conclusions can be drawn from the present results. First, cooling the vagus nerves from 37°C to 10°C lengthens Ti, as a result of the reduction of PSR activity in inflation. Second, cooling the nerves from 5°C to 0°C lengthens Te, as a result of the removal of an excitatory input from C-fibers; in this temperature range C-fiber activity is

largely blocked (Fig. 3-27). However, it seems unlikely that the lengthening of Te between 10°C and 5°C is due to removal of persisting activity in PSRs. PSR activity during the inflation phase is thought to shorten Ti and during deflation is thought to lengthen Te (Trenchard, 1977; Knox, 1973, 1979). At 10°C in the present experiments Ti had almost reached a maximum. Thus I believe that in the present experiment most PSR activity during the inflation phase had been blocked at 10°C, because further cooling the nerves had little effect on Ti. Furthermore, cooling the vagus nerves causes a reversal of rhythmic activity in low threshold PSRs, i.e. the PSR activity in deflation is still present (though greatly reduced) when activity in inflation is blocked (Paintal, 1966). Therefore, if the effects of cooling the vagus nerves between 10 and 5°C were due to removal of PSR input, a shortening Te would have been likely instead of a lengthening. I conclude that the lengthening of Te when the nerves were cooled from 10°C to 5°C was mainly due to removal of an excitatory input from RARs.

RAR input is thought to cause augmented breaths (see INTRODUCTION) and to facilitate the initiation of inspiration (Davies et al, 1981). It might be possible that RARs shorten Te by facilitating the inspiratory drive; C-fibers shorten Te by facilitating the respiratory frequency; PSRs lengthen

Te by inhibiting inspiratory mechanisms. Therefore, in normal eupnea, the two excitatory inputs from RARs and C-fibers interact with the inhibitory input from PSRs to regulate the length of Te.

INFLUENCE ON TRACHEAL SUBMUCOSAL GLAND SECRETION

Bronchoconstriction and airway secretion are important components of defense reflexes of the lungs (Coleridge and Coleridge, 1981). Though RARs have long been considered to participate in the defense reflex, their roles in bronchoconstriction and airway secretion have not been demonstrated experimentally (Coleridge and Coleridge, 1984, 1986). The results of this study on dogs support the hypothesis that pulmonary RARs cause reflex secretion by tracheal submucosal glands. Secretion was evoked by a reduction in compliance, by removal of PEEP and by application of NEEP, the stimuli being given in increasing order of effectiveness. These three stimuli did not affect PSRs or C-fibers in a consistent manner, and their effectiveness in increasing secretion was proportional to their effectiveness in stimulating RARs.

The results confirmed that the increased secretion is due to input from pulmonary afferents, i.e. due to a

reflex and not to any consequences of the mechanical maneuver. Deflation of the lungs could produce shunts, and thereby decreases arterial PO_2 and increases arterial PCO_2. Hypoxemia has been reported to increase tracheal secretion by a carotid body chemoreflex in dogs (Davis et al, 1982 a). However, in the present experiments the lungs were ventilated with 50% O_2, and blood gas analysis showed that arterial O_2 tension remained high; hence the possibility of hypoxic stimulation of arterial chemoreceptors can be excluded. Moreover, blood gas analysis showed that the experimental maneuvers had no significant effect on arterial PCO_2 and pH. Moreover effects on secretion were still obtained in experiments in which the aortic nerves were cut and the carotid regions were perfused at constant pressure with normoxic and normocapnic blood.

The recurrent and paracurrent laryngeal nerves were always cut in these experiments, so that the tracheal segment was innervated solely by the superior laryngeal nerves (Roberts et al, 1981). Hence cutting or cooling the cervical vagus nerve interrupted only the afferent limb of the reflex without interrupting the motor supply to the tracheal segment. Thus the abolition of the secretory response to NEEP by vagotomy and vagal cooling indicated that the increased secretion was due to a reflex and was vagally mediated. When the vagus nerves were cooled, and the response to

application of NEEP was abolished, stroking the laryngeal mucosa still evoked the formation of numerous hillocks, confirming that the efferent pathway for secretion was still functionally intact.

The results verified that the afferent pathway of reflexly evoked secretion is cholinergic. Submucosal glands are under parasympathetic control (Nadel et al, 1986) because stimulation of vagal efferents can increase the secretion and the effect is Ach mediated (Ueki et al, 1980). The increased secretion caused by application of NEEP in the present experiments was blocked by atropine, indicating that Ach is involved in the reflex pathway.

The present results showed that an increase in RAR activity correlated positively with an increase in the secretion rate from tracheal submucosal glands (compare Table 3-3 and Fig. 3-29). Deflation of the lungs is a potent stimulus to RARs (Knowlton and Larrabee, 1946; Armstrong and Luck, 1974; present results) and has little effect on pulmonary C-fibers (Coleridge and Coleridge, 1977; Armstrong and Luck, 1974; present results). Moreover, the secretory response was blocked when the vagus nerves were cooled to 6°C, at which temperature the conduction of impulses from RARs is blocked whereas that in C-fibers is still present. Thus we can exclude the possibility that C-fibers

had any role in the observed increase in secretion.

Since deflation of the lungs not only increases RAR activity but also reduces PSR activity (Adrian, 1933; present results), it could be argued that the graded secretory response to the different degrees of deflation (removing PEEP and applying NEEP) might be attributed to the reduction of PSR activity. However, secretion rate also increased when C_{DYN} decreased (lung stiffness increased), and increasing lung stiffness at constant tidal volume has little effect on the mean activity of PSRs (present results); indeed, if there is any effect, it is to increase PSR activity (Widdicombe, 1961) or to increase peak PSR activity (present results). Therefore, PSRs do not seem to be involved.

Furthermore, if the reduction of PSR activity were a responsible factor, baseline secretion rate would increase when the vagus nerves had been cooled to 6°C to block myelinated fibers (RARs and PSRs). However, after myelinated fibers had been blocked, baseline secretion rate decreased. This suggests that the major effect of blocking input in myelinated fibers was to remove an excitatory influence of RARs.

The present results showed that RAR activity increased several fold when lung stiffness increased by about 50 percent after deflation of the lungs. The RAR activity

adapted to a new steady level over a 2 minute period. Therefore, the 2 minute period in which secretion rate was measured coincided with the period of highest RAR activity after lung stiffness was increased. The increased secretion after lung deflation and increased lung stiffness, and the decreased secretion during vagal cooling suggest that stimulation of RARs was responsible.

The small, but statistically significant decrease in secretion after atropine suggests that there is a tonic efferent influence on baseline secretion. The fact that vagotomy (after the recurrent lanyngeal nerves were cut) produced almost the same decrease in baseline secretion as did atropine suggests that the tonic efferent activity depended on vagal afferent input. Since cooling the vagus nerves to block myelinated fibers also decreased baseline secretion to the same extent, it is reasonable to believe that at least part of the vagal afferent input is from RARs. This tonic effect in dogs is comparable to that in cats in which 39% of basal secretion was due to a tonic neural drive (Ueki et al, 1980).

Therefore, it can be concluded that: 1. rapidly adapting receptors in the lungs reflexly evoke secretion from tracheal submucosal glands in dogs; 2. the efferent arm of this reflex is muscarinic; 3. muscarinic cholinergic efferents

have a tonic influence on the baseline secretion rate which may depend on tonic RAR input.

The present results differ from those of Phipps and Richardson (1976), who on the basis of experiments in which histamine aerosol was administered in cats claimed that pulmonary RARs did not cause secretion. In their experiments, however, tracheal mucus output was measured over a 15 minute period, and it is possible that any transient increase in mucus output would be masked by the long collection period.

CONCLUSION

In this dissertation I have concentrated on the physiological role of RARs in normal lungs. I did not deal with their involvement in the reflex respiratory disturbances associated with lung disease, which has often been considered as their major functional importance (Widdicombe, 1986), although experimental evidence for the reflex function of RARs in lung disease has been scanty. The present research provides clear evidence that RARs reflexly evoke airway submucosal gland secretion and hence lend support to the suggestion that RARs have an important reflex role in pathological situations. Nevertheless, my interest was in the possibility that RARs transit useful information to the

respiratory centers under normal condition.

The fast conduction velocity of RARs together with their regular cycle to cycle respiratory modulation when the lungs become stiffer is well suited to the property of sensing mechanical changes. Moreover their reflex property of facilitating inspiratory drive would serve to match inspiratory effort to increasing lung stiffness. Although the alternative title 'irritant receptor' seems to imply a prominent sensitivity to chemical stimuli this may not be the case. Many of the responses to irritant chemicals once attributed to input from RARs may in fact be due to input from C-fibers, whose properties are more suited to sensing chemical stimuli. However, mechanical and chemical factors often coexist in pathological processes (see INTRODUCTION) and therefore, I believe that the inputs from the RARs and C-fibers act together in pathological situations.

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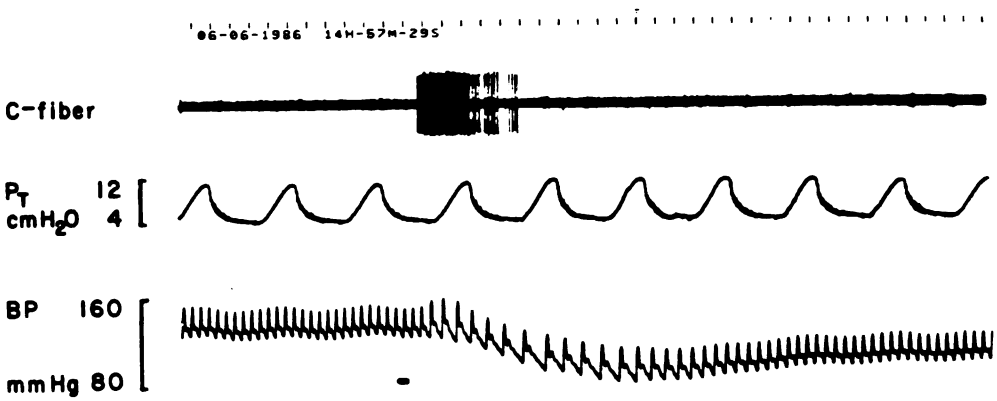

Fig. 4-2. The response of a pulmonary C-fiber to the right atrial injection of capscaicine (20 μg/kg) in a dog. The traces are C-fiber action potentials; tracheal pressure (P_T); arterial blood pressure (BP). On the top the interval beween two small dots are one sec. At the bottom the black bar is the marker for injection. Note the C-fiber responds to capscaicine with a very short latency and very high initial discharges.

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