Indian J Physiol Pharmacol 2002; 46 (3) : 264–278

REVIEW ARTICLE

AIRWAY RAPIDLY ADAPTING RECEPTORS – SENSORS OF PULMONARY EXTRA-VASCULAR FLUID VOLUME

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(Received on February 22, 2002)

Abstract : The factors regulating transfer of fluid into the pulmonary extra-vascular space and the role of sensory receptors of the airways in detecting such fluid fluxes are reviewed and discussed. It is concluded that the rapidly adapting receptors (RARs) located in apposition to bronchial venules are highly sensitive to changes in the pulmonary extra-vascular space produced by mild elevations of left atrial pressure, plasmapheresis and pulmonary lymphatic obstruction and their activation causes respiratory stimulation, an increase in tracheal tone and cough. There is a reflex diuresis also following the stimulation of these receptors by pulmonary lymphatic obstruction. It is proposed that the RARs function as a sensory component of the pulmonary defence mechanisms which preserve the 'milieu interior'.

Key words : congestion receptors vagus

INTRODUCTION

A persistent imbalance between factors which regulate the influx and efflux of fluid from the micro-circulation into the extra-vascular space results in an abnormal accumulation of fluid in the interstitial space. This condition is called edema. When it occurs in the periphery, it is unsightly but not life-threatening. However, when this process occurs in the lung, it has significant consequences and eventually threatens survival. In its final stages, fluid accumulates in the alveoli and interferes with gas exchange. It must be recognized that overt pulmonary edema, when it occurs secondary to left ventricular failure, is a late manifestation of the disease. In its early stages, fluid accumulates in the interstitial spaces of the airways (59).

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Physiological events have to be activated at the early stages so that the 'milieu interior' of the lung is preserved. For a 'sensory receptor afferent mechanism' to be a part of these events, it has to satisfy the following criteria : 1) the sensory nerve endings must be stimulated by small physiologically relevant fluid fluxes occurring in the pulmonary extra-vascular space, 2) their stimulation must produce reflex adjustments to remove the excess fluid that has accumulated in this region and 3) they must be strategically located to detect such fluid fluxes. The present review will focus upon these three aspects only. It will deal with the role of vagal sensory receptors in general and the rapidly adapting receptors (RARs) in particular, in the reflex adjustments during an expansion of pulmonary extra-vascular space produced by partial obstruction of the mitral valve, plasmapheresis and pulmonary lymphatic obstruction. It will also deal with the responses of these receptors to cardiogenic pulmonary edema produced by left ventricular dysfunction and non-cardiogenic pulmonary edema produced by chemicals which disrupt the anatomical integrity of the pulmonary micro-vasculature (permeability edema). It will not cover the events which follow high altitude pulmonary edema and neurogenic pulmonary edema.

Factors regulating fluid fluxes

There are three main factors which regulate the exchange of fluid between the micro-vasculature and the extra-vascular space. These are the hydrostatic pressure, oncotic pressure exerted by the plasma proteins and the lymph flow (61). It will also be affected by the hydraulic permeability of the vessel wall and the reflection co-efficient of the vessel wall to plasma proteins. Collectively, it is described by the equation :

$$Jv/A = Lp\ [(Pc-Pi) - \sigma\ (\Pi c-\Pi i)]$$

where Jv/A is the rate of fluid filtration or resorption per unit area of the vessel wall, Lp is the hydraulic permeability of the vessel wall, Pc and Πc are respectively the hydrostatic and oncotic pressure of plasma, Pi and Πi are respectively the hydrostatic and oncotic pressure of the interstitial fluid and σ is the reflection co-efficient of the micro-vasculature wall to plasma proteins (33). Basically, whenever there is an increase in the hydrostatic pressure of plasma or a decrease in its oncotic pressure, fluid tends to leak into the interstitium. When the nature of the filtering membrane is altered also, vessels will leak excessively. The fluid that escapes thus is drained by the lymphatic system.

Experimental methods

Extra-vascular fluid volume can be increased by overloading of the circulation with infusion of large volumes of fluid (35). Clinically, one observes this phenomenon in post-operative patients infused with excessive amounts of saline. In mitral stenosis and left heart failure also, fluid accumulates in the lung due to an increase in the back pressure in the pulmonary micro-vasculature (1). Experimentally, such a condition can be produced by surgical damage of the mitral valve (19, 69). Reversible partial obstruction of the mitral valve can be achieved in experimental animals by positioning a balloon in the left

atrium and inflating it with small volumes of saline (28, 56).

When there is a reduction in the oncotic pressure of plasma, fluid from the micro-vasculature leaks into the interstitial space. Lowered osmotic pressure causes peripheral edema but not pulmonary edema (17). In patients with chronic protein wasting diseases such as the nephrotic syndrome, edema is noted when the serum albumin level is less than 3 g/100 ml (68). However, when a lowered plasma osmotic pressure is combined with an increased pulmonary micro-vascular pressure, both become contributing factors in the development of pulmonary edema. Guyton and Lindsey (21) demonstrated that in the dog there was no significant change in the lung water content until the left atrial pressure was elevated by 23–25 mmHg. However, when they decreased the plasma protein concentration by 50%, they observed that even a left atrial pressure elevation of 11 mmHg was sufficient to increase the lung water content.

Obstruction of the lymphatics which drain the fluid away from the pulmonary interstitium also will result in fluid accumulation. The lymph from all lobes of the right lung and the upper and middle lobes of the left lung is drained mainly by the right lymphatic ducts which open into the right external jugular vein (65). When the pressure in the right external jugular vein is elevated by 15 mmHg above the basal level for a period of 2 hrs, pulmonary edema occurs in the dog (37). Experimentally, pulmonary lymphatic obstruction can be produced by creating a vascularly isolated pouch in the right external jugular vein after ligating the veins surrounding the points of entry of the lymphatic ducts (52, 64) and then pressurizing it (22, 52).

Disruption of the anatomical integrity of the pulmonary micro-vasculature by injection of chemicals also leads to accumulation of fluid in the pulmonary extra-vascular space. In suicidal attempts with organophosphate insecticides, pulmonary edema is a prominent symptom (45). In experimental animals, the two most commonly used chemicals for producing a permeability edema are alloxan and α-naphthylthiourea (3). Since pulmonary edema and respiratory failure sometimes accompany gram-negative bacterial septicemia in humans, various investigators have used *E. coli* and *Pseudomonas aeruginosa* endotoxins in the dog and sheep respectively (4, 62).

Pulmonary vagal sensory receptors

Even though there is some evidence for the existence of pulmonary receptors with sympathetic afferents (32), the sensory receptors of the lung travel mainly in the vagus nerves (8). The vagal sensory receptors have been classified into :

a) Slowly adapting pulmonary stretch receptors (SARs),

b) Rapidly adapting receptors (RARs),

c) Bronchial C-fiber receptors and

d) Pulmonary C-fiber (type J) receptors.

Among these, SARs and RARs are connected to myelinated vagal afferents. The

SARs are identified by their characteristic respiratory rhythm and slow adaptation to a maintained inflation of the lung (Fig. 1). Their conduction velocity ranges between 8–62 m/sec (41). They are located mostly in the smooth muscle layer of the airways (23, 54) and the natural stimulus for these receptors appears to be a change in tension in the wall of the airways (7). The RARs have sparse, irregular resting discharge. During a maintained lung inflation, they adapt rapidly (Fig. 1). Their conduction velocity ranges between 4–37 m/sec (41). Several studies of the past indicated that they were located superficially in the epithelial and sub-epithelial layers of the airways (10, 11). Recently, they have been shown to be present in the extra-vascular space adjacent to the bronchial venules also (58). Since irritant vapours stimulated these receptors, airway irritation was considered to be the natural stimulus for these receptors (41) when the recent studies show that their natural stimulus is more likely to be a fluid flux in the pulmonary extra-vascular space (48).

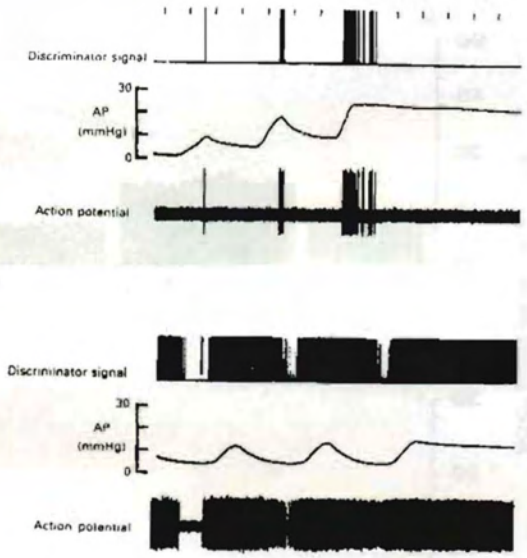

Fig. 1 : Examples of RAR (top) and SAR from a rabbit showing response to a maintained inflation. Note that during maintained inflation, the RAR alone shows rapid adaptation. The lungs were inflated for three successive breaths by occluding the expiratory port of the ventilator and at the peak of the third breath, the inspiratory port was also occluded. From above downwards, the tracings are: time marker (s), the processed signal from discriminator, airway pressure (AP) and action potentials. (Reproduced from J Physiol. 1991; 432: 81–97).

The bronchial C-fiber and pulmonary C-fiber receptors are connected to non-myelinated vagal afferents predominantly. Individual C-fibers appear to have negligible spontaneous activity and their conduction velocity ranges between 0.8–7 m/sec (41). These receptors are identified as bronchial and pulmonary C, by their respective preferential accessibility to chemicals injected into the bronchial and pulmonary circulation. The bronchial C-fiber receptors are activated by lung autacoids, bradykinin in particular (8). The pulmonary C-fiber receptors discovered originally by Paintal (39) are identified by their short latency

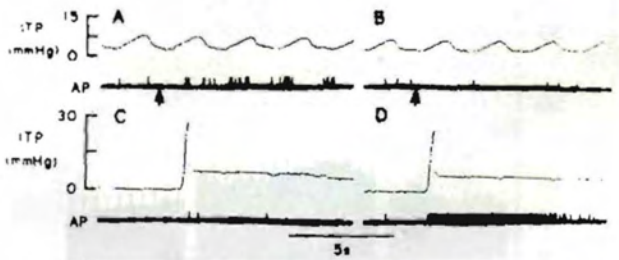

Fig. 2 : Example of a pulmonary C-fiber receptor from a monkey. A and B show respectively its response to right atrial and left atrial injections of capsaicin (20 µg/kg). Note the increase in receptor discharge in A. Capsaicin was injected at the arrows. C and D show respectively its responses to insufflation of air and halothane. Note the increase in discharge in D. ITP – intratracheal pressure; AP – action potentials. (Reproduced from Respir Physiol 1996; 106: 137–151).

responses to right atrial injections of either phenyl diguanide or capsaicin (8). They are activated by insufflation of halothane also (40, 50). An example is shown in Fig. 2. They are located in the pulmonary interstitium in between the alveoli and pulmonary capillaries (15, 25, 40) and they are stimulated by conditions which cause accumulation of fluid in this region (41).

Starling forces and pulmonary vagal sensory receptors

Effect of plasma hydrostatic pressure

A study performed in the dog systematically examined the behaviour of pulmonary vagal sensory receptors during acute elevations of left atrial pressure (28). The left atrial pressure was elevated by 10 mmHg for a period of 15 min by inflating a balloon positioned in the left atrium. This manoeuvre stimulated the SARs, RARs and bronchial C-fiber receptors significantly. However, it failed to activate the pulmonary C-fiber receptors (Fig. 3). The stimulation appeared to be greatest in the case of the RARs. Also, unlike their responses to sustained inflation (Fig. 1), the increase in RAR activity did not adapt and was maintained during the entire period of application of the stimulus (Fig. 3). This study provides convincing evidence that the

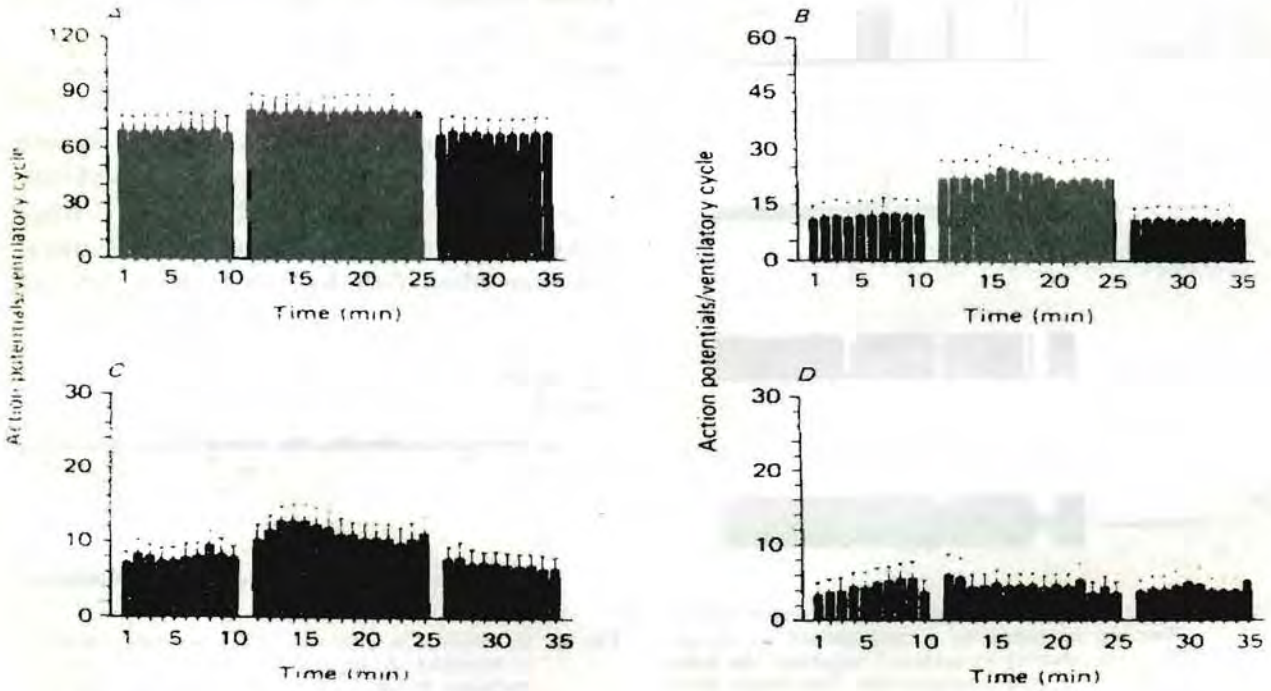

Fig. 3 : Responses of SARs (A), RARs (B), bronchial C-fiber receptors (C) and pulmonary C-fiber receptors (D) in a dog to elevation of left atrial pressure by 10 mmHg. The ordinate shows receptor activity expressed as action potentials/ventilatory cycle. The abscissa shows time in min. Note that the activities of SARs, RARs and bronchial C-fiber receptors during the period of elevation of left atrial pressure (11–25 min) are significantly different from their corresponding activities during the initial (1–10 min) and final (26–35 min) control periods ($P<0.05$). There is a greater stimulation of the RARs which shows no adaptation during the experimental period. Note also that during this manoeuvre, there is no stimulation of the pulmonary C-fiber receptors. Bars represent +SEM. (Reproduced from J Physiol 1987; 394: 249–265).

RARs respond in a non-adaptive fashion to pulmonary congestion produced by partial obstruction of the mitral valve. During obstruction of venous return from the lung, it is likely that the venous return from the bronchial mucosa is interfered also as the bronchial veins drain into the pulmonary veins (43). It was speculated that an obstruction to the bronchial venous flow would result in engorgement of the mucosal lining and stimulate the RARs (28). For such a phenomenon to happen, it is necessary to provide evidence that the stimulus applied is sufficient enough to increase the fluid flux in the pulmonary extra-vascular space.

To identify changes in the pulmonary extra-vascular fluid space, it is necessary to have a reliable method for measuring the extra-vascular water content of the lung. There are several ways of quantifying the lung water content (18). These include post-mortem desiccation of the lung (42), continuous weighing of isolated and perfused lungs (16), usage of indicator dilution techniques (5) etc. Under steady state conditions, measurement of pulmonary lymph flow is a reliable method for determining the fluid leaving the pulmonary exchange vessels and the lymph protein concentration serves as an estimate of perimicrovascular protein concentration (4). In the dog, Uhley et al., (63) cannulated the right external jugular vein, created a pouch over this cannula and collected pulmonary lymph. It is known that the lymph from the right lung and the upper and middle lobes of the left lung are drained by the main right lymphatic duct. This duct along with several accessory lymphatic ducts open into the right external jugular vein (63.65). By this method, the pulmonary lymph flow in the dog was reported to be 3.2 ml/hr (64). It is possible to collect pulmonary lymph by identifying the main right lymphatic duct and cannulating it. By the latter method, it has been found that the basal pulmonary lymph flow in the dog is 1.6 ml/hr (52). The lower value reported in this study could be because only the main right lymphatic duct is drained. Nevertheless, during elevation of left atrial pressure by 10 mmHg, there is a fourfold increase in the pulmonary lymph flow (52) which is quantitatively similar to other published reports (64). These findings establish that the stimulation of the RARs during elevation of left atrial pressure is a consequence of the fluid flux in the pulmonary extra-vascular space.

Subsequent studies performed in the dog (29), rabbit (22) and the monkey (51) have shown that for a step rise in the mean left atrial pressure, there is a step increase in RAR activity. In the rabbit, it has been reported that an elevation of left atrial pressure by 3 mmHg is sufficient to stimulate the RARs (46). Since such haemodynamic changes occur under physiological conditions like exercise (12), it appears that the physiological (natural) stimulus for the RARs is a fluid flux in the pulmonary extra-vascular space.

Effect of blockade of the clearance mechanisms

If fluid fluxes in the pulmonary extra-vascular space stimulate the RARs, it follows that experimental manipulations which prevent its lymph drainage would expand the space and stimulate the RARs. Such a manoeuvre may stimulate the pulmonary vagal sensory receptors in general and the RARs in particular. This

possibility was examined in the dog and the rabbit. Pulmonary lymphatic obstruction was produced in a reversible manner by creating an isolated venous pouch in the right external jugular vein and pressurizing it as shown in Fig. 4. This stimulus activated the RARs significantly (Fig. 5). The activation was sustained during the entire period of pulmonary lymphatic obstruction. Unlike the RARs, there was no activation of the SARs (22, 52). When the study was extended to the C-fiber receptors, pulmonary lymphatic obstruction did not stimulate the pulmonary C-fiber receptors (26). Preliminary experiments show that bronchial C-fiber receptors are not activated either (Gunawardena, Ravi, Kaufman, Longhurst and Kappagoda – unpublished observations). Thus, even though SARs and bronchial C-fiber receptors are also located in the proximal airways, it is the RAR which is capable of detecting small changes in the pulmonary extra-vascular space. It is pertinent to note that the basal pulmonary lymph flow in the rabbit is 0.35 ml/hr (24). Since the RARs were stimulated in the first few minutes of lymphatic obstruction (Fig. 5), it is conceivable that the RARs must be exquisitely sensitive to fluid accumulating in the pulmonary extra-vascular space.

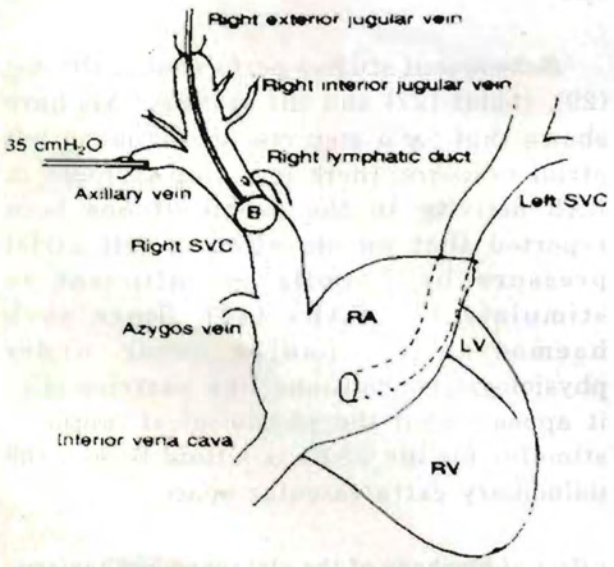

Fig. 4 : Method for reversible obstruction of pulmonary lymph flow. This was achieved by creating a pouch in the right external jugular vein after inflating the balloon (B) and by connecting the cannula in the axillary vein to a saline reservoir kept at a height of 35 cm above the right atrium. Pulmonary lymphatic obstruction was relieved by deflating the balloon and lowering the level of the reservoir to that of the right atrium. The rest of the venous tributories was ligated. RA – right atrium, RV – right ventricle, SVC – superior vena cava. (Reproduced from *J Physiol* 1997; 503: 833–840.

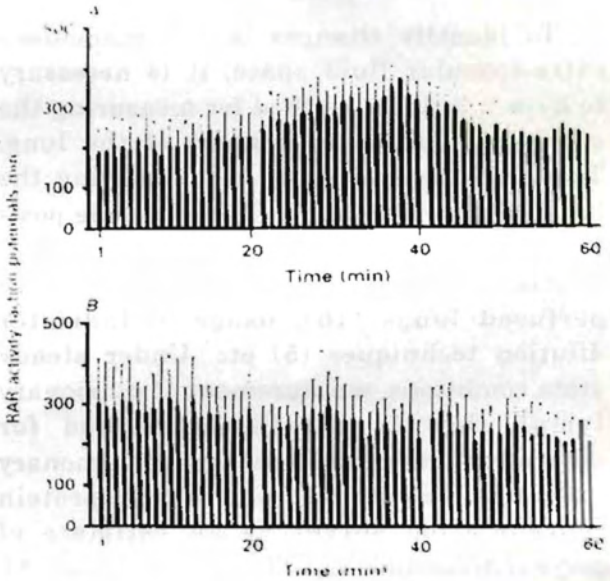

Fig. 5 : Responses of RARs to pulmonary lymphatic obstruction in rabbits. A – effect of pulmonary lymphatic obstruction on the activity of RARs. Activities during the initial control period (1–20 min), during lymphatic obstruction (21–40 min) and the final control period (41–60 min) are shown. The activity during the period of lymphatic obstruction was significantly greater than those during the control periods ($P<0.05$). B – spontaneous variation in the activities of RARs with time. RAR activity was recorded continuously for 60 min. Note that the increase in RAR activity observed during pulmonary lymphatic obstruction in A is different from the changes attributable to spontaneous variation. Bars represent +SEM. (Reproduced from *J Physiol* 1991; 432: 81–97).

Effect of plasma oncotic pressure

As defined by the Starling equation, another factor which regulates fluid exchange is plasma oncotic pressure. In the dog (29) and rabbit (22), the plasma protein concentration was reduced by 15–20% by batch plasmapheresis. Such a reduction would decrease the plasma oncotic pressure by 30% approximately (38). Plasmapheresis increased the resting activity of the RARs (22, 50). Also, it augmented the increase in RAR activity produced by pulmonary lymphatic obstruction (46). The stimulus-response curve relating left atrial pressure and RAR activity was elevated upwards and shifted to the left when performed in the background of plasmapheresis (22, 29) (Fig. 6). Similar effects were not seen on the activities of SARs (22, 29) and C-fiber receptors (Gunawardena, Ravi, Kaufman, Longhurst and Kappagoda - unpublished observations). Collection of pulmonary lymph showed that elevation of left atrial pressure augmented the increase in basal flow observed after plasmapheresis (29).

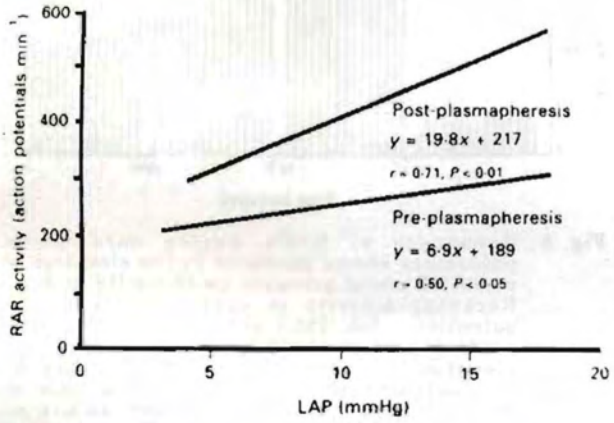

Fig. 6: Regression lines relating mean left atrial pressure (LAP) and RAR activity (expressed as action potentials/min) elicited before plasmapheresis (lower line) and after plasmapheresis (upper line). The slope and intercept of the upper line were significantly different from the lower line. (Reproduced from *J Physiol* 1991; 432: 81–97).

Taken collectively, these findings show that among the sensory receptors of the airways, the RARs are stimulated maximally by small manipulations of the different components of the Starling forces regulating fluid fluxes in the pulmonary extra-vascular space. Thus, in the early stages of pulmonary edema when fluid accumulates mostly in the proximal airways (60), the RARs function as a major sensory pathway and initiate reflexes which may protect the lung.

Pulmonary edema

There are two major types of pulmonary edema-non-cardiogenic and cardiogenic. Non-cardiogenic edema which includes permeability edema also can be produced by volume overload. Inhalation of toxic gases (eg. chlorine, phosgene) causes a direct lesion of the alveolar membranes. Also they make the adjoining blood vessels leaky, resulting in permeability edema. Intravenous administration of chemicals such as alloxan and α-naphthylthiourea also produce permeability edema. It has been suggested that liberation of chemicals such as histamine, bradykinin and serotonin in the lung may cause pulmonary edema. Pietra and Fishman (43) demonstrated that histamine and bradykinin cause bronchial edema preferentially. Cardiogenic pulmonary edema occurs in a great variety of clinical conditions-aortic insufficiency, mitral insufficiency and hypertensive heart disease.

While recording from pulmonary C-fiber receptors, Paintal (40) demonstrated that the activity of these receptors increased following the injection of alloxan or inhalation of chlorine gas. Occlusion of atrio-ventricular junction also stimulated them. Roberts et al., (53) observed that during volume overload, there was a marked stimulation of these receptors. Even though RARs and SARs were also stimulated, these authors reported that during interstitial edema, the pulmonary C-fiber receptors alone were activated. Thus, there is compelling evidence that during non-cardiogenic pulmonary edema, the pulmonary C-fiber receptors are clearly stimulated.

In a study performed in the dog, Coleridge and Coleridge (6) demonstrated that during transient elevation of left atrial pressure to > 20 mmHg, there was a stimulation of pulmonary C-fiber receptors. Ravi and Kappagoda (49) produced cardiogenic pulmonary edema by elevating the left atrial pressure by 20–25 mmHg for a period of 45 min and showed that there was an intense stimulation of these receptors during this period. Thus, cardiogenic edema is also a potent stimulus for these receptors.

Pulmonary edema activates the RARs also profoundly. Whether the edema is caused by volume overload (53), administration of alloxan (49) (Fig. 7) or mitral insufficiency (49) (Fig. 8), there is an intense stimulation of these receptors.

The evidences presented thus far suggest

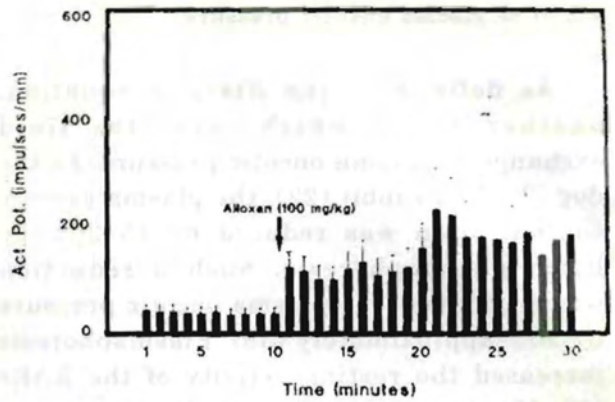

Fig. 7: Responses of RARs to a non-cardiogenic pulmonary edema produced by the injection of alloxan (100 mg/kg, i.v.) in dogs. Alloxan was injected at the arrow. Receptor activity is expressed as action potentials (Act. Pot.) per minute during the control period (1–10 min) and following the injection of alloxan (11–30 min). Note the increase in RAR activity which is maintained during the entire recording period. Bars represent +SEM. (Reproduced from *Can J Physiol and Pharmacol* 1992; 70: 68–76).

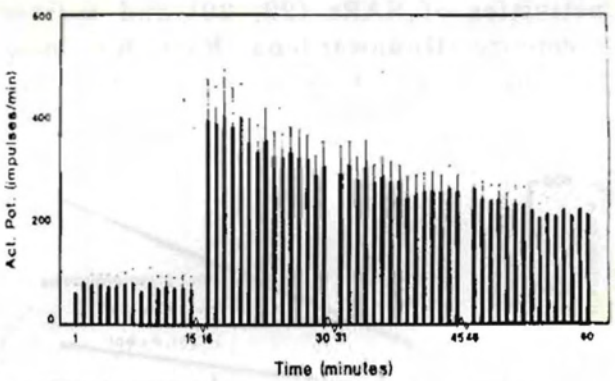

Fig. 8: Responses of RARs during cardiogenic pulmonary edema produced by the elevation of mean left atrial pressure by 25 mmHg in dogs. Receptor activity is expressed as action potentials (Act. Pot.) per minute during the control period (1–15 min) and during the elevation of mean left atrial pressure by 25 mmHg (16–60 min). Note the increase in RAR activity during the entire 45 min of elevation of left atrial pressure. Note also that the increase in activity which is maximal in the first 15 min declines gradually with time. Even then, the activity during the final 15 min (46–60 min) period is significantly higher than the activity during the control period ($P<0.05$). Bars represent +SEM. (Reproduced from *Can J Physiol and Pharmacol* 1992; 70: 68–76).

that before pulmonary edema ensues, there is an intervening stage in which fluid diffuses/leaks into the extra-vascular space from where it is cleared by pulmonary lymphatics. When the capacity of the lymphatics to drain this fluid is exceeded, it tends to accumulate. This process is augmented when there is a decrease in the oncotic pressure of plasma. It is proposed that during these early stages, there is a predominant activation of RARs and their activation causes the respiratory stimulation (30), tracheal contraction (27) and cough (66) seen in patients during pulmonary congestion (1). As the congestion is permitted to progress, overt pulmonary edema occurs and along with the RARs, there is a significant stimulation of the C-fiber receptors. Together, these two groups of receptors account for the respiratory symptoms seen in pulmonary edema.

Maintenance of body water balance

It is well recognized that in heart failure, there are alterations in renal function which result in fluid retention (1). The pulmonary edema that occurs on ascent to high altitude has also been considered to be in part due to the diminished urine output from the kidneys (36, 57).

Cardiopulmonary receptors play a role in maintaining body fluid volume. Acute elevations of left atrial pressure stimulate the left atrial receptors (41) and cause an increase in urine flow (34). This response is one of the compensatory mechanisms associated with the early stages of left ventricular failure. Like the atrial receptors, the sensory receptors of the lung may also regulate body fluid volume by interfering with the renal function.

RARs and urine flow

Ideally, when a receptor - afferent system is sensitive to a particular stimulus, it is natural to expect that it will produce a reflex response which will remove the stimulus that caused its activation. The material reviewed thus far suggests that among the pulmonary vagal sensory receptors, the RARs are exquisitely sensitive to fluid fluxes in the pulmonary extra-vascular space. Thus, it is expected that their stimulation should activate mechanisms which remove the excessive fluid in the lung. One way by which this goal can be achieved is by interfering with renal function.

Recent studies in the rabbit show that during pulmonary lymphatic obstruction, there is a reflex increase in urine flow (47) (Fig. 9). This response gets abolished on cooling the cervical vagi to 8°C suggesting that it is due to stimulation of receptors with myelinated vagal afferents. Pulmonary lymphatic obstruction does not cause any significant change in heart rate, mean arterial blood pressure and central venous pressure (47). Hence it is unlikely that there will be the involvement of high and low pressure receptors of the cardiovascular system. Since pulmonary lymphatic obstruction stimulates the RARs selectively, the increase in urine flow is presumably due to the activation of the RARs.

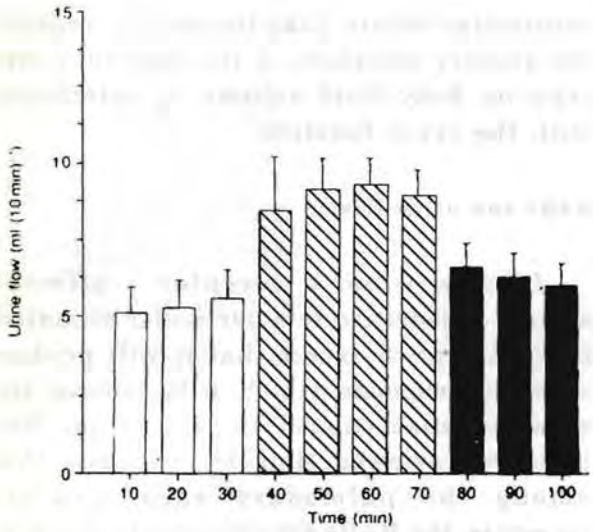

Fig. 9: Changes in urine flow during pulmonary lymphatic obstruction in rabbits. Mean urine flow (ml/10 min) during the initial control period (10, 20 and 30 min, □), during the period of pulmonary lymphatic obstruction (40, 50 and 60 min, ▨) and during the final control period (70, 80, 90 and 100 min, ■). The urine collected during the 70 min period is included as part of the response. The increase in urine flow observed during the period of pulmonary lymphatic obstruction was significantly different from those during the control period ($P<0.025$). Bars are +SEM. (Reproduced from *J Physiol* 1997; 503(3): 833–840).

The increase in urine flow observed during pulmonary lymphatic obstruction is abolished by sectioning of the renal nerves. This finding is in contrast to the atrial receptor induced diuresis wherein it has been shown that during elevation of left atrial pressure, there is an inhibition of renal nerve activity (39). The precise mechanism by which the RARs with vagal afferents integrate with the renal nerves to produce a diuretic response remains to be elucidated. It is possible that there may be excitation of renal sympathetics during pulmonary lymphatic obstruction. But, the catecholamines liberated from these nerve endings generally cause fluid retention by promoting renal vasoconstriction (44). However, direct measurements of total and regional (cortical and medullary) blood flows to the kidney showed no significant changes during pulmonary lymphatic obstruction (2). These results suggest that a change in blood flow may have only a minor role to play in this diuretic response. Preliminary experiments indicate that nitric oxide may be involved in this process as the response is abolished by prior administration of L-NAME (Gunawardena, Ravi, Bravo and Kappagoda-unpublished observations). It is proposed that the nitric oxide liberated locally from the sympathetic nerve endings may interfere with the renal tubular reabsorptive mechanisms which promote sodium excretion and diuresis.

Location

For a sensory mechanism to respond to fluid movements, it should be strategically located to detect fluid fluxes occurring in its environment.

It is now well known that the RARs are stimulated by the inhalation of a variety of irritant vapours. These include ammonia, cigarette smoke, alcohol, acetone and ether (51, 67). Based upon these findings, it was proposed that the epithelial and sub-epithelial nerve endings of the airways described by Elftman (13), were the counterparts of RARs. Subsequent electron microscopic studies showed that these endings were connected to vagal myelinated fibers (10, 11). Thus, the RARs may have a superficial location in the airway.

There is evidence that the RARs may be located in the deeper layers of the airways.

For instance it was reported that the responses of the RARs to inflation persisted even after stripping of the airway mucosa (55). During the inhalation of bupivacaine aerosol, the RARs were found to be less readily blocked compared to the SARs (14). Recent electrophysiological investigations reveal that in the deeper layer, the RARs may be located in apposition to bronchial venules (58).

The bronchial veins form plexuses on either side of the bronchial muscles which are linked by transmuscular venous channels. As the bronchi divide and sub-divide, they eventually lose the cartilage and the muscle layer becomes attenuated. In these regions, the two plexuses approximate each other, fuse and merge with pulmonary veins (43). In the bronchial interstitial space, in the sub-mucosal layer, there are the capillaries and venules of the sub-mucosal plexus, connective tissue containing mast cells and small lymphatic vessels. The muscular layer is perforated by arterial and venous radicles to and from the peribronchial plexus (43). In the peribronchial interstitium are larger venules, big lymphatic vessels and nerve trunks.

The electrophysiological experiments indicated that the RARs may be located in the deeper layer also in close proximity to the bronchial venules (48). Indeed, electron microscopic investigations in the rat have revealed the presence of sensory nerve endings connected to myelinated vagal afferents in this region (58) (Fig. 10).

Thus, the RARs may have a dual location, one superficial and another deeper. The receptors in the superficial layer will respond readily to inhaled irritant vapours and to inflammatory mediators. Those located deeply would respond to changes in the bronchial interstitium.

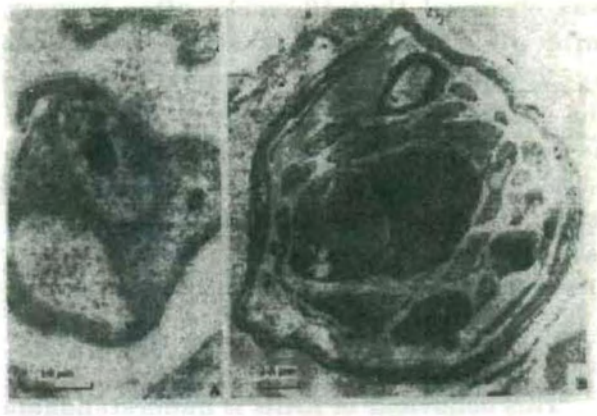

Fig. 10 : A. Electron micrograph of an encapsulated nerve terminal near a bronchial venule showing HRP reaction product inside an unmyelinated axon in a rat bronchus.

B. Electron micrograph of an encapsulated nerve terminal near a bronchial venule showing degenerating axon profiles (myelinated and unmyelinated) 3 days after cervical vagotomy in a rat. (A and B reproduced from *J Anat* 1990; 168: 265–276).

RARs in a diseased state

The evidences presented thus far suggest that during acute changes in the pulmonary extra-vascular space there is a significant activation of the RARs. But, what happens to the behaviour of these receptors in a chronic diseased state namely sustained elevation of left atrial pressure as in left ventricular failure is not known. A recent study examined the behaviour of RARs in a rabbit model of mitral regurgitation (19, 20). In that study, chronic pulmonary venous congestion was produced surgically by partial destruction of the mitral valve. It

was observed that 12 weeks after surgery, mild elevations of left atrial pressures by 5 and 10 mmHg did not stimulate the RARs. However, these receptors could be stimulated by a left atrial pressure > 20 mmHg (19, 20). The sensitivity of RARs to mild elevations of left atrial pressures could be restored by shrinkage of the extra-vascular fluid compartment by administering hypertonic albumin.

This behaviour of RARs is understandable since in the chronic state, even though the basal extra-vascular fluid content of the proximal airways was found to be increased, the left atrial pressure had to be raised by 20 mmHg or so in order to produce a change in the extra-vascular fluid volume similar to that produced by elevation of left atrial pressure by 10 mmHg in normal control rabbits. These results show clearly that for producing an increase in RAR activity, there has to be a change in the extra-vascular fluid volume *per se*. Following partial damage to the mitral valve, fluid will tend to diffuse into the interstitium and the RARs would have responded with an increase in activity. As the condition is permitted to progress, a steady state would be reached and the RARs would have got adapted to this stimulus. Thus, there may not be a significant increase in the basal activity of RARs (19, 20). The failure of RARs to respond to mild elevations of left atrial pressure in this state is probably because the fluid fluxes which occurred were proportionately smaller compared to the normal intact rabbits. Clinically, left ventricular failure is characterized by a state of chronic pulmonary venous congestion with intermittent episodes of pulmonary alveolar edema (1). During these episodes, the RARs may function as an important additional afferent mechanism for the respiratory symptoms.

ACKNOWLEDGEMENTS

The work reported in this review is supported by grants from NIH, USA (to C.T. Kappagoda) and ICMR, New Delhi (to K. Ravi).

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