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COMMENTARY

THE LUNG AS AN ENDOCRINE ORGAN

R. R. BEN-HARARI* and M. B. H. YOUDIM
Technion, Faculty of Medicine, Department of Pharmacology, P.O. Box 9649, Haifa 31096, Israel

In order for any organ to be classified as an endocrine gland certain unifying principles or criteria must be fulfilled. It is not likely that these criteria could be defined in a manner entirely acceptable to all biologists since there are still many points of dispute. In this paper a broader, perhaps more flexible definition than that of Bayliss and Starling [1] has been taken, which must also undergo change as new information becomes available. The various subheadings within the text are the criteria which we feel are necessary to classify any organ as an endocrine gland.

Endocrine glands secrete biologically active substances called hormones and therefore before defining the properties of an endocrine gland it is necessary to define the properties of a hormone. A hormone is defined as: a chemical messenger or regulator, secreted by living cells, usually in trace amounts, and is normally transported by the blood to specific sites of action in the organism where it is not used as a source of energy, but acts to regulate reactions in order to bring about an appropriate response by the organism. This working definition of a hormone as a substance secreted into the bloodstream may not be strictly true. Although the majority of hormones are secreted (produced and emitted) by endocrine glands, other hormones, such as β-lipotropin and angiotensin II (AII) are formed from precursors in the circulation. Furthermore, metabolism of biologically active substances by an organ such as the liver or lung also controls the hormonal composition of circulating blood by adding or removing these substances. Consequently, the biological activities of organs distant from the site of metabolism are regulated. Thus, confining the definition of a hormone to a chemical which is only secreted is unduly restrictive. Such metabolic functions can therefore be regarded as also serving an endocrine function.

Although metabolic functions are not unique to the lung it is essential to the concept of the lung as an endocrine organ that its activities take place at the centre of the circulation. There is one further very important difference between the lung and other metabolic organs, such as the liver, selectivity. Despite having a full complement of enzyme activities the lung, unlike the liver, has evolved an elaborate system of specific uptake, enzyme specificities and partitioning of its enzymes, thus conferring on the lung the attribute of specificity. As a result the lung can distinguish within a chemical group of hormones [2, 3]. This is clearly illustrated by comparing the metabolism of the amines 5-hydroxytryptamine (5-HT), noradrenaline (NA), dopamine and tyramine in the lung and liver. Despite an overall similarity in their capacity (enzyme activities and affinities) to deaminate these amines, catabolism in the lung, but not in the liver, was shown to be limited by its uptake into the cell [4, 5]. There are many other examples of the specific processing of hormones by the lung. For example, NA is taken up readily by the lung but its methylated homologue, adrenaline (ADR), is not; prostaglandins (PGs) of the E- and F-series are metabolised as they pass through the pulmonary circulation but prostaglandins of the A-series and PGI_2 pass intact through the lungs. AII is inactivated on passage across every systemic vascular bed, except that of the lung. Thus, the lung does not simply play the role of a metabolic organ, as the liver does [5, 6]. Instead, the specific handling of hormones implies that the lung has a specific role in controlling the level of hormones circulating in the blood.

Although the first publications indicating an active metabolic function of lung appeared in the 1920s [7, 8], it was not until the 1960s that Vane and his colleagues demonstrated the role of the lung in processing biologically active substances. It was from this period of investigation that the present concept of the lung both as a metabolic and as an endocrine organ originated. Vane [9] classified vasoactive hormones into two types—'local' and 'circulating' hormones. The local hormones, e.g. NA, 5-HT and PGE_2 were those which were effectively removed by the lung and their physiological function is probably localised at or near the site of release. This proposal can now be qualified by the earlier statements on the definition of a hormone. The circulating hormones were those which pass through the lung unchanged, e.g. ADR, AII and PGI_2, or those with an increase in activity, e.g. angiostensin I (AI), and act at a systemic site distant from the lung.

The question 'Is the lung a paraendocrine organ?' was finally posed by Ryan and Ryan [10], but these authors mainly restricted their answer to the processing of polypeptide hormones by the pulmonary circulation. The processing of polypeptide hormones by the lung is part of the more general classification of what has become known as the non-respiratory (or the metabolic) functions of the lung, the various aspects of which can be found in a variety of excellent

* Present address of author to whom correspondence should be addressed: Dr R. R. Ben-Harari, University of Miami School of Medicine, Pulmonary Research Division (R120), P.O. Box 016960, Miami, FL 33101, U.S.A.

reviews [3, 11–14]. These reviews have all substantiated the endocrine nature of the lung.

However, a more systematic approach as attempted in this paper, employing criteria to define the lung as an endocrine organ, has not been made previously. It is not within the scope of this article to describe the biochemistry and physiology of the various hormones we will refer to, the means by which they are transported in the bloodstream, their metabolism and their mechanism of action at target sites. Such information can be found in recent reviews of endocrinology. Also we have not attempted to cover exhaustively the available literature demonstrating that the lung is an endocrine organ. Rather, we have endeavoured to present what is in our opinion the most crucial evidence from a variety of sources, including original articles and reviews.

The endocrine glands are the most highly vascularised tissues in the body

The pulmonary circulation is ideally suited for its purpose as an endocrine gland by virtue of its enormous blood supply (it receives the total cardiac output), its strategic position interposed between mixed venous blood and the systemic arterial blood and its enormous capillary bed of tiny-calibre vessels presenting a vast surface area ($\sim 70\ m^2$) for blood–tissue interaction [15, 16]. These very same properties which facilitate gas exchange in the lung also help the exchange of hormones between the endothelium and the blood. As a result the lung can modify the hormonal composition of the entire systemic blood supply.

Endocrine glands are generally composed of several different cell types possessing unique cellular and subcellular specialisations

Most endocrine glands contain several functionally different populations of types of cells. For example, the pars distalis of the pituitary is composed of at least five different hormone secreting cells: somatotrophs (growth hormone); lactotrophs (prolactin); corticotrophs (ACTH); gonadotrophs (FSH and LH); and thyrotrophs (TSH). Electron micrographic and biochemical studies have provided information on the manner in which various cell organelles from gland cells have specialised in order to participate in the secretory process. For example, steroid-secreting cells, such as those of the gonads and adrenal cortex, contain a very extensive smooth endoplasmic reticulum which is frequently arranged into extensive whorl patterns and the Golgi complex is typically very prominent [17].

The lung is composed of approximately 40 different cell types [18], but of these only a small number are known to possess either the localisation, biochemical activities or structural properties necessary for endocrine function. The first suggestion that the lung contained endocrine cells was made by Feyrter [19]. The epithelium lining the airways contains a population of cells with morphological and biochemical characteristics suggesting endocrine functions [20, 21]. These cells are known by a variety of names including Feyrter cells, Kultschitsky cells, neuroendocrine or neurosecretory cells, enterochromaffin cells, AFG (argyrophil-fluorescent-granulated) cells and APUD (amine content, amine-precursor uptake and decarboxylation) cells [22]. In the lung these cells occur either singly or in small clusters and are found in many other endocrine organs including the pituitary, thyroid, pancreatic islets and adrenal medulla [20]. The cells are now known to contain the peptides bombesin [22, 23], calcitonin and leu-enkephalin [23] and amines, are are capable of taking up amine precursors and synthesising amines [24]. The physiological or endocrine function of the lung airway endocrine cells is unknown. However, their likely endocrine, or perhaps neuroendocrine role is emphasised by their rich efferent and afferent innervation [25, 26] and their fine-structural similarities to cells composing oat-cell carcinomas [27, 28] and certain interneurones found in sympathetic ganglia [29, 30].

Cells in the lung, other than APUD cells, may also possess such a neurosecretory role. Vasoactive intestinal peptide (VIP), a hormone which occurs widely in the nervous system and G.I. tract [31, 32] has a predominantly neural distribution in the lung, being localised in nerve cell bodies and fibres in the walls of bronchi, in relation to the secretory glands and smooth muscle, in pulmonary and bronchial vessels as well as in ganglion-like structures in peribronchial connective tissue [33, 34]. The following progressive changes are thought to have occurred in the evolution of regulatory mechanisms resulting in the formation of an endocrine gland: intracellular messengers → nerve cells → neurosecretory cells → endocrine glands [35]. Although this hypothesis is theoretical, it may be considered to suggest that these neurosecretory cells in the lung underwent phylogenic development specialising them as a diffuse endocrine organ.

Lymphoid tissue is also present in the lung and extends throughout the respiratory tract from the nasopharynx to the alveolar ducts. The lymphatic apparatus includes hilar lymph nodes typical of those found in other lymphatic tissues, lymphoid nodules in large and medium-sized bronchi infiltrated with lymphocytes and lymphoid aggregates in peripheral lung tissue consisting of lymphocytes, macrophages and granulocytes (for review and references see Ref. 36). Pulmonary lymphatic tissue is responsible for the synthesis of immunoglobulins (Igs) occurring in the lung and evidence indicates that antibody generated in the lung contributes to the systemic vascular pool of Igs. Synthesis of the different subclasses is performed by lymphocytes in the lamina propria and submucosa of the bronchi and interstitial tissue. Although it is not clear that these cells are generated locally, it is clear that these cells are capable of Ig synthesis and secretion and reside in the lung.

All pulmonary vessels are lined with an extremely thin (0.5 μm), single-cell layer of endothelial cells of the continuous type. Although these cells have no unusual organelles, the luminal surface of endothelial cells of the pulmonary artery and smaller vessels, including capillaries, is covered with a profuse array of finger-like projections [16]. In addition to the surface projections, pulmonary endothelial cells contain enormous numbers of caveolae intracellulares (pinocytic vesselS; ~10,000–15,000 per cell;

70 nm in diameter), a large proportion of which (70%) communicate directly with the vascular lumen [37, 38], the remainder being located in the cytoplasm. Both the caveolae and the projections have the effect of almost doubling [38] the surface area. Thus, the localisation directly facing the vascular lumen, and their structural specialisations, make endothelial cells especially well-suited for the processing of blood-borne substances and for the rapid return and addition of products to the circulation.

Endocrine glands influence homeostatic mechanisms of the body

A major function of the endocrine system is to maintain the constancy of the internal environment. Maintenance of homeostatic mechanisms by the lung is mediated through the effects of either circulating hormones or possibly by circulating metabolites of intermediary metabolism. Evidence will be presented demonstrating that dysfunction of the lung as a result of disease alters the state of homeostasis, revealing that the lung under normal conditions helps maintain homeostatic mechanisms.

The contribution of the lung to metabolic substrate turnover has yet to be firmly established. However, the lung may make a significant contribution to whole-body lactate and alanine turnover [39] and in patients with chronic lung disease there is a change in the circulating levels of metabolites of intermediary metabolism, e.g. lactate, pyruvate and glycerol [39].

The mammalian lung can generate, degrade, activate and release into the circulation hormones whose wide spectrum of biological activities can influence the functions of distant organs and of the lung itself. The processing of hormones covers a broad range of types of compounds including steroids, biogenic monoamines, prostaglandins, polypeptide hormones and adenine nucleotides. Thus, the lung controls to some extent the normal hormonal composition of the blood.

The pulmonary endothelium provides a vast surface area for the exchange of hormones between lung and blood. It also forms an important interface between flowing blood and the coagulant activity of the underlying adventitial and medial layers of the vessel wall preventing platelet aggregation, and also participates in vascular homeostasis. The metabolism of ADP by the lung is complex [40, 41]. ADP is degraded to AMP and then to adenosine by enzymes on the luminal surface of endothelial cells [42–44]. Much of the adenosine is then taken up intracellularly where part of it is converted to inosine. Some of the inosine is returned to the extracellular space and the remainder is incorporated into intracellular ADP and ATP. Thus, the lung can inactivate the platelet-aggregating agent ADP [45] and release into the vascular space adenosine which is capable of inhibiting platelet aggregation [45]. Adenosine is also thought to play a contributory role in producing functional vasodilatation [46].

Prostanoids are not only degraded by the lung but they are also generated and secreted by this organ [47]. The main products via the cyclooxygenase pathway in the lung are PGI_2 and thromboxane A_2 (TXA_2) [48]. PGI_2 is continuously secreted by the lung *in vivo* [49, 50] and completely survives passages through the pulmonary circulation [51, 52]. PGI_2 relaxes arteries and prevents blood platelets from aggregating [53, 54], and it has been postulated to have a very important role in the control of platelet aggregation and atherogenesis [55]. TXA_2, by contrast, is a potent inducer of platelet aggregation and constrictor of arterial smooth muscle [56].

The endothelium of the lung may make a further contribution to the control of blood coagulation and play yet an additional role, this time in fibrinolysis. The exact physiological mechanisms by which coagulation and fibrinolysis are regulated remain unknown. Many factors control these processes some of which have been associated with the lung and

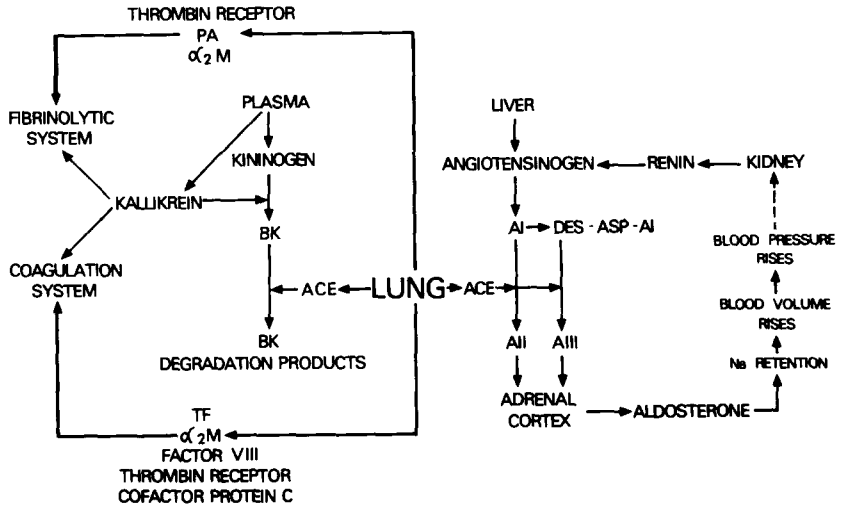

Fig. 1. Control by the lung of: (a) the negative feedback system (broken line) existing for the angiotensinogen → angiotensin → aldosterone system, and (b) the fibrinolytic and coagulation systems (ACE = angiotensin-converting enzyme; AI, AII and AIII = angiotensin I, II and III; BK = bradykinin; PA = plasminogen activator; α_2M = α_2-macroglobulin; TF = tissue factor antigen).

pulmonary endothelium (Fig. 1). Endothelial cells of pulmonary arteries and arterioles contain plasminogen activator, a factor capable of initiating fibrinolysis [57, 58]. Plasminogen activator has been demonstrated in the membrane-rich fraction of endothelial cells from the rabbit vena cava [59] and is both synthesised and secreted by these cells. An additional factor, located on the surface of endothelial cells, which has anti-coagulatory properties is a cofactor for accelerating thrombin-catalysed protein C activation [60, 61]. Protein C inhibits clot formation by inactivating factor Va [62] and factor VIIIa [63], and platelet-supported clotting by inactivating the platelet receptor for factor Xa [64, 65]. In addition, protein C markedly enhances clot lysis [66, 67]. This co-factor activity is unique to the endothelium among vascular tissues [61].

Thromboplastin or tissue factor antigen occurs on plasma membranes of pulmonary arterial endothelial cells [68] and this factor activates the extrinsic clotting pathway. In cultured endothelial cells from human umbilical vein, tissue factor is both synthesised and secreted [69]. Factor VIII antigen has been localised on the capillary endothelium of the lung [70] and factor VIII antigen [71] and factor VIII von Willebrand factor [72] are synthesised and secreted by cultured human umbilical vein endothelial cells. α_2-Macroglobulin has been demonstrated on the luminal surface of human vascular endothelial cells [73]. Specific high-affinity binding sites for thrombin have been demonstrated *in vivo* in the rabbit lung [74] and the rapidity with which thrombin is cleared by the lung indicates that the binding sites exist on endothelial cells. Many similarities exist between thrombin binding *in vivo* and in cultured endothelial cells from the human umbilical vein [75]. These binding sites are then thought to catalyse the inactivation of the pro-coagulatory thrombin by antithrombin III [74]. Since heparin sulphate has been found in large quantities on cultured endothelial cells [76] and thrombin has been shown to bind heparin [77–79] it was proposed that a heparin-like substance may be the receptor on endothelial cells [74].

Whether all these fibrinolytic, coagulant and anti-coagulant activities are located, synthesised or secreted by pulmonary endothelial cells has not yet been sufficiently investigated. Their importance in the lung cannot be underestimated in view of the fact that all these activities have been localised to the vascular endothelium and that the endothelium of the lung comprises approximately 50% of the total endothelial cells in the body [38]. These factors may complement the effects of PGI_2 and the adenine nucleotides on platelet aggregation. Such a relationship is strengthened by the reports that thrombin can cause release of PGI_2 from the endothelium [80–82]. Taken collectively, these observations suggest that the lung and in particular pulmonary vascular endothelial cells contribute to the control of thrombosis. That the lung may be important in thrombosis is seen in patients with adult respiratory distress syndrome when there are disturbances of clotting and fibrinolysis resulting in disseminated intravascular coagulation [83–85].

Another factor possibly involved in modulation of vascular homeostasis is a growth factor synthesised and secreted from endothelial cells [86, 87]. This endothelial cell-derived growth factor (EDGF) causes the proliferation of smooth muscle cells in culture. Since an early event in the development of arteriosclerotic lesions is the migration of smooth muscle cells from the media to the intima and smooth muscle proliferation [88], EDGF is attractive as a candidate to play these same two roles *in vivo*. A further possible function of EDGF as a circulating factor might be in the process of forming or repairing blood vessels. Endothelial cells are the first cell to appear in the wall of a new blood vessel and smooth muscle cells appear later [89, 90].

In terms of processing of the polypeptide hormones it is evident that the lung plays a central role in regulating the overall functioning of the renin–angiotensin–aldosterone system, the kallikrein–kinin system and vascular tone. The enzyme angiotensin-converting enzyme (ACE) [91, 92], located on the plasma membrane of endothelial cells [93, 94], catalyses the conversion of AI to AII. Another physiologically active peptide formed from AI in the lung is des-Asp-AII or angiotensin III (AIII) [95, 96]. AIII is active on vascular smooth muscle and in stimulating aldosterone secretion from the adrenal cortex [96–99]. The two pathways for AIII to be formed in the lung [95] are shown in Fig. 1. Either pathway requires ACE so that any changes in ACE activity would be reflected in changes in production of AIII and AII and thus in aldosterone secretion. Fig. 1 shows a scheme of how the lung plays a key role in the renin–angiotensin–aldosterone system proposed to control blood pressure. The control of aldosterone secretion by the adrenal cortex is a classical example of a negative feedback system, the most common mechanism employed by endocrine glands to control secretion. Within this system the lung operates a metabolic control by which the input to the system is the inactive pro-hormone AI and the output is conversion to the active substances AII and AIII.

The peptide bradykinin (BK) is also inactivated by ACE on passage across the lung [92]. The ability of the lung to eliminate a hormone which lowers the blood pressure (BK) while forming a hormone which raises the blood pressure (AII) strongly suggests that the lung may play a direct role in blood pressure homeostasis. AII and BK are also capable of inducing the release of PGI_2 and TXA_2 from the lung [100, 101] and from pulmonary endothelial cells [102]. This presents an alternative mechanism by which BK, AII and the lung can affect the blood flow. In fact, patients with lung disease have alterations in blood pressure homeostasis [103].

Both BK and AII have been implicated in other circulatory changes. BK [104] and AII [105, 106] are thought to produce necessary circulatory adaptations in the perinatal period. If the lung regulates the arterial concentrations of vasoactive substances changes occurring in vasoactive hormone levels during the perinatal period should be reflected in lung activity. Pulmonary ACE activity, measured with AI, and pulmonary bradykininase activity measured with BK, rise over the last third of gestation in the rabbit [107].

Control of endocrine gland activities

Not only do endocrine glands influence homeostatic mechanisms but the activities of endocrine glands are in turn influenced by homeostatic mechanisms. With the exception of the adrenal medulla and posterior pituitary complex, other endocrine glands do not depend upon direct nervous control. The activities of endocrine glands are regulated mainly by chemical means or interoreceptive stimuli, e.g. the pH, osmolarity, glucose, the oxygen concentration and hormones, in contrast to exteroreceptive stimuli, e.g. auditory, visual, olfactory, thermal and tactile.

The regulation of endocrine activities of the lung by hormones has been the most extensively studied. The substrates of intermediary metabolism are altered in response to hormones. Insulin [108–112], glucocorticoids and ACTH [108, 113], and catecholamines [108] all influence glucose utilisation by the lung. Insulin has also been shown to increase the rate of pulmonary amino acid uptake [114] and to decrease the rate of protein degradation [115] in lungs. Since the endocrine system is highly integrated, any perturbation, such as the deficiency of hormones normally present, leads to profound changes in the function of the other glands. In lungs from diabetic rats, glucose utilisation is diminished but can be reversed with insulin [112, 116]. Lungs from rats rendered hypothyroid, diabetic or adrenal insufficient have an increased capacity to generate cyclic GMP *in vitro*. Treatment of hypothyroid rats with triiodothyronine and of diabetic rats with insulin restored cGMP production rate to normal. Dexamethasone treatment of adrenalectomised rats had no corrective effects, but addition of steroid hormones to lung slices from adrenalectomised–gonadectomised rats restored cGMP production [117]. Since the circulating concentrations, uptake and disposal of these substrates by the lung are under endocrine control, there is a potential indirect mechanism for one or several hormones to influence the metabolism or activity of another hormone. It is established that agents which alter the levels of cAMP and cGMP alter the immunological release of hormones from the lung [118, 119]. Cyclic AMP has also been implicated in the release of plasminogen activator in some cell systems [120, 121]. Thus changes in cyclic nucleotide levels in the lung may alter the activity of the lung in blood coagulation. Changes in the active processing of hormones such as 5-HT [122–124] also occur. Clearance of 5-HT in the lung is decreased by the metabolic inhibitor 2-deoxyglucose and is reversed by adding substrates such as lactate and pyruvate [125].

There is also evidence for a more direct interaction between hormones and the lung in the control of the lung's endocrine functions. The oestrous cycle and administration of the ovarian steroids, oestradiol and progesterone, markedly affect the inactivation of the amines 5-HT [126] and β-phenylethylamine (PEA) [127], and of the peptides BK and AI [128, 129], in the lung of rats. The uptake, metabolism and generation of prostaglandins by the lung is affected by glucocorticoids, sex steroids, pregnancy, hyperthyroidism, ovariectomy and adrenalectomy [130–134] and during the oestrous cycle [135]. The fact that the endocrine functions of the lung are influenced by the endocrine control systems of the rest of the body, which in turn are influenced by the endocrine activities of the lung, reveal that the lung is an integral part of the endocrine system.

The control of integration within the endocrine system is provided by the anterior pituitary or 'master gland'. The anterior pituitary regulates the activity of endocrine glands by secreting tropic hormones which induce hypertrophy and hyperplasia in the target gland. The majority of the hormones described affecting the metabolic–endocrine functions of the lung are under the regulation of the pituitary gland. Thus, it is conceivable that the lung, also as an endocrine organ, is under the control of the pituitary by means of tropic hormones such as prolactin and ACTH, as shown in Fig. 2. In support of this proposal functions of the lung other than metabolism have been shown to be associated with the activity of the pituitary. During acromegaly [136] and hypopituitarism [137] lung respiratory mechanics were altered and under the influence of the pituitary growth hormone the lung can be induced to grow [138]. The foetal lung has been a renewed focus of interest of endocrinologists for the past two decades since Liggins [139] suggested that glucocorticoids promote foetal lung maturation and the early appearance of lung surfactant. The foetal lung, like many other differentiating tissues, is subject to regulation by hormones including corticosteroids [140], ACTH [141], thyroid hormones [142–144], oestradiol [145] and prolactin [146]. The involvement of the pituitary in this regulation of surfactant production has been shown after decapitation [141, 147, 148], hydranencephaly, produced by ligation of both carotid arteries [149], and hypophysectomy [150], all of which delayed lung maturation. Replacement therapy with ACTH [141] or dexamethasone [151] helped restore normal lung maturation.

It is clear from the data described so far that not

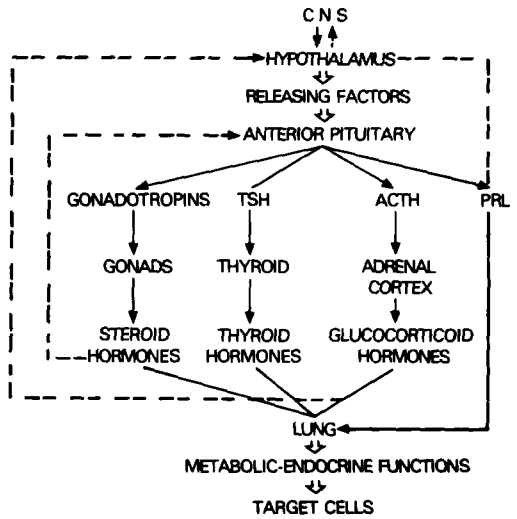

Fig. 2. Endocrine control achieved by hypothalamus → anterior pituitary → endocrine gland → target cell hierarchy (- - - -, negative feedback).

only does the lung behave like an endocrine organ but it has also been shown to be a target organ for other hormones secreted by other endocrine glands. Hormones are generally secreted in low concentrations and are recognized by specific tissues (target organs) which respond in a specific fashion. The mechanism of action of a hormone involves its initial interaction with receptor sites of the target cells. For the majority of hormones that have been shown to affect various lung functions, binding to the lung has been shown to occur via specific receptors.

Lung cell receptors have so far been described for the hormones oestradiol [152–155], progesterone [156], glucocorticoids [140], thyroid hormones [156, 157], insulin [158], prolactin [159–161] and for β-adrenergic agonists [162, 163]. The activities of several receptors mentioned are also under regulation by hormones. In male rats during postnatal development the concentration of androgen receptors in the lung increased during the peri-pubertal period, while oestrogen receptor activity was high before puberty and decreased after puberty [153]. In female rats, concentrations of androgen and oestrogen receptors in the lung were influenced during the oestrous cycle [153]. All these changes in receptor level correlated well with changes in the blood levels of androgen and oestrogen.

The receptors to most of these hormones mentioned might be expected to be found on pulmonary endothelial cells, because the majority of the lung functions influenced by the hormones have been localised to the pulmonary endothelium. But to-date no studies have been performed on pulmonary endothelial cells. However, receptors have been demonstrated for oestradiol [164] and indirectly for other hormones [165] in non-pulmonary endothelial cells in culture.

Hormones are not the only stimuli known to control the endocrine functions of the lung. Exposure to high oxygen tensions (hyperoxia) has received a great deal of attention because of its widespread clinical use and its selective toxicity to the lung at atmospheric pressures [166–168]. Low oxygen tension or hypoxia is also clinically important since it is associated with a variety of clinical conditions such as chronic bronchitis and emphysema [169]. After both hyperoxia and hypoxia, the endothelial lining of the pulmonary circulation shows overt changes [170, 171]. Hyperoxia diminishes the pulmonary metabolism of prostaglandin E_2 [172, 173], AI and BK [173], and 5-HT and PEA [173–175], and uptake of 5-HT by cultured endothelial cells [176]. Hypoxia modulates ACE activity both *in vivo* [177, 178] and in cultured endothelial cells [179].

After exposure to hypoxia the APUD cells secrete their amine-rich vesicles by exocytosis [180, 181] establishing the secretory nature of the APUD cells. The other neurosecretory cells, containing VIP, release this bioactive substance during anaphylaxis [182]. Ventilation has long been recognized as a stimulus for release of prostaglandins from the lung [183]. Intermediary metabolism in the lung, which indirectly may control endocrine functions of the lung, also responds to hypo- and hyperventilation, hypoxia and hyperoxia, and to other stimuli including changes in pH and pCO_2 [39].

Malfunction of endocrine glands results in systemic disorders

A necessary corollary to an endocrine gland showing adaptive changes to the individual requirements of the organism is that any aberration in these functions may result in disease. In the text we have attempted to describe some of the contributions played by particular lung functions to homeostatic mechanisms and how homeostasis may be altered if lung functions become altered in conditions such as disease. There are many examples of lung dysfunction and disease many of which have not been included in the text for the sake of brevity. However, the manifestations of dysfunction of the lung may be divided into two groups. The first group are syndromes due to ectopic secretion of hormones most commonly associated with bronchogenic tumours, such as oat-cell carcinoma. Hormones secreted include ACTH, corticotropin-releasing factor, melanocyte-stimulating hormone, 5-HT, ADH, LH, FSH, HCG, HPL, HGH, insulin, glucagon and prolactin. Secondly, pulmonary and systemic disorders involving alteration of the normal levels of humoral agents released from the lung (for review of these two groups see Refs. 184–186). Diseases of the lung possibly related to release of humoral agents are associated with systemic disorders of the neuromuscular, vascular, gastrointestinal, coagulation and fibrinolytic systems and of skin and connective tissue. The diseases of the lung include anaphylaxis, pulmonary embolism, hyperventilation and respiratory alkalosis, pulmonary oedema, emphysema and adult respiratory distress syndrome. The hormones originating from the lung believed to mediate these systemic disorders include biogenic amines, polypeptides and prostanoids.

An understanding of all these processes is of clinical importance. One area where metabolic–endocrinologic studies may contribute to clinical applications is in the early diagnosis of lung tumours [187]. Although the hope of a specific marker of malignant change, such as ACTH or any other hormonal secretion of the lung, has not yet been fulfilled, the usefulness of continuing research in this area is invaluable. Other biochemical changes, such as in 5-HT, PEA and PGE_2 metabolism in the lung, have been offered as indicators of early oxygen toxicity to the lung [173–175]. In chronic granulomatous diseases such as sarcoidosis [188–190] serum ACE levels rise markedly, most likely reflecting damage to lung endothelial cells. For the time being, ACE has provided a useful biochemical marker of disease and emphasises the fruitfulness of this area of research.

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