The Lung—An Endocrine Organ?

S. I. Said*

There is increasing evidence that the lung may perform a number of metabolic activities which are characteristic of endocrine organs. One of these activities, to be reviewed here, is the ability to influence important, biologically active humoral substances in a variety of ways, including synthesis, storage, release, inactivation and activation.

I. Pulmonary Synthesis and Release of Vasoactive Hormones.

A. Histamine and Other Mediators of Anaphylaxis:

During anaphylaxis and other immediate hypersensitivity reactions, such as attacks of extrinsic asthma, a number of potent substances are released from the lung, and these are largely responsible for the clinical manifestations of these disorders. The mediators of anaphylaxis include histamine, "slow reacting substances of anaphylaxis (SRS-A)", bradykinin, and certain prostaglandins (PG's). The major source of these pharmacologically active substances (especially histamine) is the mast cells, which are abundantly present in the lung, but polymorphonuclear leukocytes and possibly other cells contribute.

The immunologic release of mediators is influenced by neurogenic and humoral factors. Thus, release is inhibited by: β-adrenergic stimulation, α-adrenergic blockade, prostaglandin E compounds, methylxanthines, and atropine. On the other hand, mediator release is enhanced by α-adrenergic stimulation, β-blockade, and cholinergic stimulation. These influences are apparently exerted through alterations in the intracellular levels of cyclic GMP, an increase in the former opposing release, and in the latter promoting it.

B. Prostaglandins:

The lung plays a major role in the metabolism of these biologically active lipids. Biosynthesis of these compounds occurs in the lung under normal conditions, and may be accelerated markedly under the influence of various stimuli. Among the conditions that may promote increased pulmonary synthesis of prostaglandins, and their subsequent release into the circulation, are, besides the previously mentioned anaphylaxis: mechanical ventilation at large volumes, respiratory alkalosis, pulmonary embolism, and pulmonary edema.

Evidence for PG release in these conditions is derived from animal experiments. In some cases, e.g., hyperventilation, the dominant compounds released are of the E variety, whereas in other instances, e.g., anaphylaxis, PGF's predominate. The effects of PG release depend on the types and amounts of PG's discharged from the lung. Thus, PGE's, vasodilators and bronchodilators, may contribute to the systemic.

*The University of Texas Southwestern Medical School and Veterans Administration Hospital, Dallas, Texas, U.S.A.
hypotension of hyperventilation and pulmonary embolism, and PGF's which have the opposite effect on vascular and bronchial smooth muscle, may cause or accentuate bronchoconstriction in asthma.

C. Vasoactive polypeptides:

Since the lung contains a kallikrein-like enzyme and has a high level of kininogen, it is potentially a rich source of kinins. One of these, bradykinin, is believed to be among the mediators of experimental anaphylaxis.

Although no other vasoactive peptides have been identified as humoral secretions of the lung, at least one peptide has been extracted and partially purified from normal hog lung. This peptide dilates systemic and pulmonary vessels, and relaxes several non-vascular smooth muscle organs. Its actions are not mediated by adrenergic or cholinergic receptors, but its possible role in physiologic or pathologic states is unknown.

II. Pulmonary Metabolism of Vasoactive Hormones

A. Biogenic amines:

The lung effectively removes serotonin (5-hydroxytryptamine) from the circulation, by uptake and inactivation.

Mammalian lung also has a high content of N-methyl transferase, an enzyme which catalyzes the metabolism of histamine. However, the lung apparently plays a relatively minor role in the inactivation of histamine in vivo, in comparison to the liver and kidney.

Of the catecholamines, norepinephrine is partially (30-40%) inactivated during passage through the lung, but epinephrine is unaffected.

B. Prostaglandins:

The metabolic influence of the lung on prostaglandins is not limited to their synthesis and release (see above): the lung is also the major site of their inactivation. This inactivation is accomplished principally through the action of a specific enzyme, which oxidizes the PG molecule at the 15-carbon position, 15-hydroxyprostaglandin dehydrogenase. The pulmonary metabolism of PG compounds is selective; while PGE's and PGF's are effectively inactivated, PGA's emerge from the pulmonary circulation with relatively little loss of activity.

C. Polypeptides and proteins:

1) Proteolytic enzymes: Not only is the lung a source of kallikrein and of kininogen, it is also rich in an enzyme (Trasylol) that inhibits several kinds of the proteolytic enzymes, kallikreins. The significance of kallikrein-kinin metabolism in lung physiology or disease remains unknown.

2) Bradykinin: This biologically potent nonapeptide is almost completely removed in one passage through the lung. Although kininases (enzymes which destroy bradykinin) are widely distributed in many tissues, bradykinin is inactivated by the lung more effectively than by any other organ. The enzymatic destruction of bradykinin may be accomplished by removal of either the C-terminal amino acid residue (kininase I) or the C-terminal dipeptide (kininase II).

As in the case of PG's, the pulmonary destruction of kinins is a selective process: compounds that are chemically related to bradykinin, such as eledoisin, physalaemin and "substance P", are not metabolized by the lung.

3) Angiotensin: The conversion of the relatively inactive decapeptide, angiotensin I, to angiotensin II provides the only known example of activation of a hormone by the lung. The conversion, which is more effective than that occurring in blood, is accomplished by the splitting off of the C-terminal dipeptide, leaving the more potent 8-residue peptide, angiotensin II.

Similarities between the pulmonary metabolism of bradykinin and of angiotensin:

a) Bradykinin and angiotensin I disappear almost completely in one circulation through the lung.
b) The inactivation of bradykinin and the activation of angiotensin I may be accomplished by the removal of the C-terminal dipeptide.

c) Both enzymatic processes apparently take place in the plasma membrane of the pulmonary capillary endothelial cells.

d) Some factors which potentiate the action of bradykinin (e.g., peptides from certain snake venoms), also inhibit angiotensin I-converting enzyme.

These considerations make it likely that the lung contains an enzyme which can catalyze both reactions; an enzyme with such activity (a dipeptide hydrolase) has recently been prepared from lung tissue.

4) Other peptides: The posterior pituitary hormones, vasopressin and oxytocin, are not metabolized by the lung. Nor is the newly isolated vasoactive intestinal polypeptide, which appears to be largely inactivated in the liver. Quantitative data are not available on the extent of pulmonary inactivation, if any, of other polypeptide hormones.

III. Hormonal Influences on Respiratory Function

Many of the humoral substances discussed above, as well as others, can, in turn, influence the function and structure of the lung. This influence can be wide-ranging and may follow one or more of these mechanisms.

A. Smooth muscle of bronchi and pulmonary vessels:

1) Bronchodilation (catecholamines, PGE compounds, vasoactive intestinal peptide "VIP" and vasoactive lung peptide, "VLP")

2) Bronchoconstriction (histamine, PGF$_{2\alpha}$)

3) Vasodilation (PGF, VIP, VLP)

4) Vasoconstriction (nor-epinephrine, PGF$_{2\alpha}$)

B. Ventilation:

1) VIP is capable of stimulating respiration in experimental animals, independently of its hypotensive effect. Since this peptide is normally inactivated in the liver, failure of its inactivation may occur in hepatic cirrhosis. The resultant presence of the peptide in the systemic circulation may explain the hyperventilation, as well as the vasodilation and increased output, often associated with that condition.

2) A number of bronchoactive agents, through their effects on bronchial and alveolar duct caliber, may also affect overall alveolar ventilation.

3) The hyperventilation of late pregnancy has been ascribed to increased blood levels of progesterone. This hormone may also have a protective ability against some form of experimental emphysema.

C. Maturation of lung and secretion of surfactant:

1) In experimental animals, intra-fetal infusions of ACTH or glucocorticoids (cortisol, dexamethasone or 9α-fluoroprednisolone) accelerates functional maturation of the lungs, and induces the premature production and secretion of alveolar surfactant. The cell maturation selectively affects the type II alveolar cell, as manifested by a sudden increase in osmiophilic inclusion bodies, which are the probable precursors of surfactant.

2) A similar effect on the functional and anatomic maturation of alveolar type II cells has been demonstrated for thyroid hormone in the rat.

IV. Conclusion

Although there is strong evidence that the lung can participate in the metabolism of vasoactive hormones, the significance of this metabolic activity of the lung, either in health or disease, remains
unknown. For one thing, most of the information now available is based on experiments in isolated organs or in animals. This information must be verified in human subjects.

The selective ability of the lung to take up, retain, inactivate or activate certain hormones may, like other functions of the lung, become altered in diseases of the lung and the pulmonary circulation. It is possible, therefore, that such alteration may reflect the presence of particular disorders of the lung. Conversely, disturbances in the pulmonary metabolism of vasoactive substances (eg, failure of inactivation or excessive release) may itself be a factor in the pathogenesis or mediation of certain pulmonary or extra-pulmonary diseases.

Summary of lecture delivered before the Japanese Society of Chest Disease, Fukuoka City, April 4, 1973. A more detailed paper on the same subject, with numerous references, is now in press in Federation Proceedings.