Metabolic Functions of the Pulmonary Circulation

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THE primary function of the pulmonary circulation is to bring the blood in contact with alveolar gas, for the purpose of gas exchange. In addition to this vital function, in which the lung may be said to play a "passive" role, the pulmonary circulation has another, more recently recognized function. This is an "active," or metabolic, function, in which the lung takes up, inactivates, or activates certain circulating compounds, and synthesizes and releases others. These metabolic activities help determine and regulate such important functions as pulmonary vascular and airway smooth muscle tone, pulmonary microvascular permeability, regional and total pulmonary blood flow, and systemic arterial blood pressure.

In the few past years, the pace of research on lung metabolism has accelerated, and several reviews and monographs have been published on the subject (Said, 1968; Vane, 1969; Bakhle and Vane, 1974, 1977; Junod, 1975; Said, 1979; Ciba Symposium, 1980). This paper focuses on the metabolism and release of vasoactive hormones and neurotransmitters and the role that these activities may play in the physiological regulation and the pathophysiological responses of the pulmonary circulation.

Uptake and Metabolism of Biologically Active Compounds

Compounds That are Taken Up and Degraded by Intracellular Enzymes (Fig. 1)

Serotonin (5-Hydroxytryptamine). Possibly the first indication of the metabolic potential of the pulmonary circulation was the observation in 1925, by Starling and Verney, that a "serum vasoconstrictor substance was detoxicated" on passage through a heart-lung preparation. This vasoconstrictor substance was identified later as serotonin (5-hydroxytryptamine) (Rapport et al., 1948), which was subsequently shown to be inactivated by perfused cat lungs (Gaddum et al., 1953). Efficient removal of serotonin by the lung has since been confirmed in many mammalian species, including humans (Thomas and Vane, 1967; Alabaster and Bakhle, 1970; Alabaster, 1977; Gillis and Roth, 1977). The extent of this removal, by isolated lung or in vivo, has been estimated to be as much as 98% (with intravenous infusion) or as low as 33% (with a bolus injection) of the serotonin reaching the pulmonary circulation, with most estimates being close to the higher figure.

The pulmonary handling of serotonin depends on uptake, followed by enzymatic degradation (Pickett et al., 1975). Because the inactivating enzyme, monoamine oxidase (MAO), is an intracellular (mitochondrial) enzyme, serotonin must cross the cell membrane to be acted upon. Only one metabolite, 5-hydroxyindoleactic acid, is detected in lung perfusate after infusion of serotonin through isolated lungs, confirming the MAO is the only metabolizing enzyme. The rate-limiting step in the pulmonary removal of serotonin, however, is not its enzymatic inactivation but its uptake into the cell. This process of uptake is saturable, energy dependent, and involves a sodium carrier system (Junod, 1972). If the process of uptake alone is inhibited, as by cocaine or by one of the tricyclic antidepressant drugs (which also inhibit its uptake in platelets), the pulmonary removal of serotonin is greatly reduced. If, on the other hand, monoamine oxidase activity is inhibited, as by mbenazine, iproniazid, or paraglyline, serotonin still is taken up and reappears slowly in the effluent from the lung.

By contrast to the uptake of serotonin by the lung, which is followed by rapid enzymatic degradation, serotonin taken up into platelets and neurons is bound and stored in intracellular membrane-bound granules. Reserpine, which inhibits the accumulation of serotonin in platelets and in neurons, does not affect its removal by the lung.

Evidence from radioautographic experiments and fluorescence microscopy suggests that the sites of uptake of serotonin in the lung are in the endothelial cells of pulmonary vessels, especially pulmonary arterioles and capillaries (Strum and Junod, 1972). The lung is also capable of forming serotonin, by decarboxylation of 5-hydroxytryptophan. This biosynthesis occurs in cells which apparently do not partic-
Figure 1. Pulmonary handling of biologically active compounds: Serotonin, norepinephrine, PGE$_2$, PGF$_2$\alpha, and probably also the leukotrienes (slow-reacting substance), are taken up from the circulation and metabolized by intracellular enzymes (see text).

SEROTONIN
NOREPINEPHRINE
PGE$_2$, PGF$_2$\alpha
LEUKOTRIENES

Paragraph:

ipate in removing serotonin. They are found in the tracheobronchial tree, and can be identified by fluorescence and other characteristic histochemical features (Pearse, 1968; Lauweryns and Cokelaere, 1973).

The actions of serotonin include airway constriction and pulmonary vasoconstriction. Its efficient uptake and inactivation by the lung is thus a useful protective mechanism that minimizes its untoward effects when it is released under abnormal conditions, such as pulmonary embolism.

Catecholamines. Approximately 30% of norepinephrine is removed in the pulmonary circulation by an uptake process similar to that of serotonin.

Unlike neuronal uptake of norepinephrine (Uptake 1),* pulmonary uptake is followed by metabolism, by the intracellular enzymes MAO and catechol-O-methyltransferase. In this respect, the uptake by the lung resembles that by extraneuronal tissues, such as the heart (Uptake 2),* but differs in having a higher affinity (lower K$_m$) (Gillis and Roth, 1976). Further, although epinephrine and isoproterenol are better substrates for the extraneuronal Uptake 2 process, neither of these catecholamines is taken up by the lung (Alabaster, 1977).

As for serotonin, the uptake of norepinephrine occurs mainly in pulmonary vascular endothelium, with preferential uptake in the pre- and postcapillary vessels and in veins (Nicholas et al., 1974). Pharmacological evidence suggests that the uptake sites for norepinephrine and for serotonin are distinct and separable (Iwasawa and Gillis, 1974).

The possible physiological significance of the differential handling by the lung of norepinephrine on the one hand (20% removal) and epinephrine or isoproterenol on the other (no uptake) is at present unknown.

Histamine. The lungs of different species contain histamine-metabolizing enzymes, including imidazole-N-methyltransferase and diamine oxidase. Therefore, it is not surprising that homogenized or chopped lung readily inactivates histamine. Relatively few reports are available on the clearance of histamine by intact lungs; most of these reports conclude that removal of histamine is ineffective, probably because of the lack of a specific transport (uptake) mechanism. A recent paper, however, showed that $^{14}$C-histamine could be taken up and metabolized by rat lungs in vivo (Krell et al., 1978).

If pulmonary inactivation in vivo is, in fact, inadequate, it means that the airways and pulmonary (and bronchial) vessels are vulnerable to the actions of endogenously released histamine, including bronchoconstriction and increased microvascular permeability.

General Comments on the Uptake of Vasoactive Amines

The foregoing discussion underscores the critical role of the uptake process in the pulmonary handling of vasoactive amines. Compounds for which this mechanism is lacking may be inactivated by lung homogenates in vitro, but not by perfused lungs or lungs in vivo. As examples, perfused lung does not inactivate epinephrine, dopamine, or tyramine, even though all are good substrates for intracellular enzymes from the lung. The uptake mechanism thus enables the lung to exercise selective control over the metabolism of these compounds (Youdim et al., 1980).

Such selectivity is not exhibited by the liver, where these and other amines (including histamine) are metabolized equally well by mitochondrial MAO pre-
The cellular sites of PG uptake and inactivation remain unknown. Ody et al. (1979) found that endothelial cell preparations derived from pulmonary artery or aorta failed to degrade either PGF\textsubscript{2\alpha}, or PGA\textsubscript{1} though they formed the previously demonstrated PGA-glutathione conjugate (Gross and Gillis, 1976). They also found evidence for selective metabolism of PGA\textsubscript{1} by smooth muscle from trachea, pulmonary artery, or aorta.

5RS-A (leukotriene C\textsubscript{4} and D\textsubscript{4}) appears to lose its biological activity (assayed on guinea pig ileum) during a single passage through the pulmonary circulation (Piper et al., 1981), but the mechanism of this inactivation remains unknown. The pulmonary metabolism of thromboxane A\textsubscript{2} has not been investigated, owing to the intrinsic instability of this compound and because it has generally been available only in semipurified preparations (Moncada and Vane, 1979). Prostacyclin (PGI\textsubscript{2}) is not significantly metabolized in the pulmonary circulation (see below).

The efficient, though selective, pulmonary removal of prostaglandins and related lipids has important potential implications to pulmonary and systemic function. Compounds like PGE\textsubscript{2}, PGF\textsubscript{2\alpha}, and the leukotrienes are rendered essentially "local hormones," acting mainly at the sites of their synthesis and release. On the other hand, PGA\textsubscript{2} and prostacyclin, which escape pulmonary inactivation, are circulating hormones capable of influencing organs beyond those where they are released.

### Compounds That are Metabolized at the Pulmonary Endothelial Surface (Fig. 2)

#### Bradykinin and Angiotensin

Ferreira and Vane (1967) showed that 80% of the bradykinin introduced into the venous blood was removed in one passage through cat lungs. Similarly effective inactivation of bradykinin by the lung has been demonstrated in several other mammalian species. About the same time, Ng and Vane (1968) reported that conversion of the relatively inactive angiotensin I into the potent vasopressor angiotensin II occurred more rapidly in the lung than in blood or other tissues.

The enzymic inactivation of bradykinin in the lung is achieved by kininase II, or dipeptidyl carboxypeptidase (EC 3.4.15.1). This membrane-bound enzyme, located in pulmonary endothelium and elsewhere, breaks peptidyl-dipeptide bonds from the carboxyl terminal end (Erdős and Yang, 1966; Yang and Erdős, 1967).

In 1956, Skeggs and co-workers discovered an enzyme in plasma that removes the carboxyl terminal dipeptide, histidyl-leucine, from angiotensin I, converting it to the octapeptide angiotensin II. They called it angiotensin I-converting enzymes. Several observations suggested that the pulmonary inactivation of bradykinin and conversion of angiotensin I to angiotensin II might be catalyzed by one and the same enzyme. Yang and co-workers, first using partially purified enzyme preparations and specific inhibitors, and later using antibody to the enzyme and homo-
A homogeneous enzyme, established the identity of angiotensin I-converting enzyme with kininase II (Erdös, 1979a).

In addition to bradykinin and angiotensin I, other endogenous substrates of this enzyme are the enkephalins (Erdös et al., 1978) and insulin, at least in vitro. Peptides that are not hydrolyzed by this enzyme include those with a penultimate proline residue (e.g., angiotensin II), those lacking a free carboxy-terminal carboxyl group, and those smaller than a tripeptide (Cushman et al., 1979).

Angiotensin-converting enzyme is located in pulmonary vascular endothelium (Ryan et al., 1976), and to some extent in the endothelium of peripheral vascular beds (Caldwell et al., 1976). The enzyme also occurs in some epithelial cells, such as the brush border of the renal proximal tubule (Ward et al., 1977) and intestinal mucosa (Ward et al., 1980). Even though the concentration of the enzyme in pulmonary endothelium is not higher than in all other tissues, the large area of the pulmonary vascular bed, to which the entire cardiac output is accessible, gives high physiological significance to the potential for angiotensin conversion in the pulmonary circulation.

Low levels of kininase II (converting enzyme) activity are found in plasma and other biological fluids (Yang and Erdös, 1967). This activity is elevated in sarcoidosis, but not in tuberculosis (Lieberman, 1975); the elevation may result from increased enzyme activity in lymph nodes. Acute hypoxia decreases pulmonary kininase II activity in dogs (Stalcup et al., 1979).

The discovery that peptides from the venom of Bothrops jararaca and other snakes potentiate the action of bradykinin and inhibit the conversion of angiotensin I has stimulated a lively interest in developing inhibitors of the enzyme for therapeutic use. Inhibitors are now available that have greater specificity and potency (Cushman et al., 1979; Erdös, 1979b), and some, including captopril, are effective by mouth. These inhibitors are now under active investigation for their usefulness as antihypertensive drugs.

Other Peptides. Substance P, an 11-residue peptide present in the central nervous system and peripheral nerves, including those in the lung, intestine and other organs, is inactivated by cultured endothelial cells from human umbilical cord and lung (Johnson and Erdös, 1977), but inactivation of substance P by whole lung appears to be ineffective. Endothelial cells in culture also inactivate leucine and methionine enkephalins (Erdös et al., 1978).

Adenine Nucleotides. Adenosine triphosphate (ATP), diphosphate (ADP), and monophosphate (AMP) are removed in one passage through the lung. The metabolizing enzymes, 5'-nucleotidase and ATPase, have been localized on the pulmonary endothelial surface and within the pinocytotic vesicles of endothelial cells (Ryan and Ryan, 1977). Dieterle et al. (1978) have demonstrated the ability of cultured endothelial cells of pulmonary and systemic origins to metabolize ATP and adenosine.

Compounds That are Neither Taken Up nor Metabolized in the Pulmonary Circulation (Fig. 3)

Compounds for which no uptake (transport) mechanism exists in pulmonary endothelium or those not metabolized by enzymes at the endothelial surface emerge from the lung without appreciable alteration or loss of activity. Reference has already been made in this review to some of these compounds, including epinephrine, dopamine, tyramine, and possibly also histamine; prostaglandin A compounds (except a proportion of which may form an adduct with glutathione); and a number of peptide hormones, such as substance P, oxytocin, vasopressin, angiotensin II (Bakhle and Vane, 1974) and vasoactive intestinal peptide (VIP) (Kitamura et al., 1975). Some pulmonary degradation of angiotensin II may occur during pul-
monary edema, possibly because of the release of intracellular metabolizing angiotensinas from endothelial and other cells (Kumamoto et al., 1981).

The biological activity of prostacyclin is not significantly reduced during passage through the lung (Armstrong et al., 1978; Waldman et al., 1978; Dusting et al., 1978), and this conclusion is consistent with biochemical evidence of only slight metabolic degradation of this compound in the lung (Wong et al., 1978). Thus, in contrast to PGE2, PGF2α, and the leukotrienes; prostacyclin is mainly a circulating hormone (Moncada et al., 1978; Gryglewski, 1979).

Effects of Physiological and Pathological Factors on Pulmonary Metabolism of Vasoactive Hormones

The pulmonary handling of vasoactive amines and of prostaglandins is subject to a variety of physiological influences. Among these are steroids, pregnancy, and the estrus cycle. Thus, the uptake of monoamines by rat lung is highest during pro-estrus, and MAO activity is stimulated by progesterone and estradiol (Youdim et al., 1980). Pulmonary inactivation of PGE2 by rabbit lung is enhanced 3-fold during pregnancy or progesterone treatment (Bedwani and Marley, 1975; Boura and Murphy, 1978).

The effects of two types of environmental factors have been investigated: oxygen and other oxidants, and cigarette smoke. The possible inhibitory effect of oxygen was first suggested by the finding (Kistler et al., 1967) that pulmonary endothelial cells were particularly vulnerable to damage during the development of oxygen toxicity. Exposure to 100% O2 for 48 hours, or to 46 ppm nitrogen dioxide for 6 hours, inhibited the metabolism of PGF2α by guinea pig lungs in vitro (Chaudhari et al., 1979), and of PGE2 by perfused rat lung (Klein et al., 1978; Bakhle et al., 1979). Hyperoxia (97% O2 for 18 hours or longer) also inhibited the uptake of serotonin by perfused rat lungs (Block and Fisher, 1977). Exposure of rats to cigarette smoke for up to 10 days suppressed the inactivation of PGE2, increased the conversion of angiotensin I to angiotensin II, but did not affect serotonin metabolism in the isolated perfused lung (Bakhle et al., 1979).

The mechanism by which oxygen might diminish serotonin and prostaglandin metabolism could involve the inactivation of enzymic SH groups. There are eight moles of sulfhydryl (SH) per mol of MAO, and the SH content appears to be important for full catalytic activity, since the oxidation of SH to disulphide bonds leads to a reduction in enzymic activity (Youdim et al., 1980). Indirect evidence suggests that 15-hydroxy prostaglandin dehydrogenase, the key enzyme in the pulmonary inactivation of prostaglandins, also contains SH groups essential for its activity (Hansen, 1976). The effect of high oxygen pressure on the transport process for prostaglandins is at present difficult to evaluate (Youdim et al., 1980).

Pulmonary Generation of Biologically Active Compounds

Many of the biologically active compounds already discussed in relation to their pulmonary metabolism may also be synthesized and released by the lung. Specially mentioned in this review, because of recent important discoveries, are histamine, vasoactive peptides, and prostaglandins and related lipids. Enzymes and other proteins, e.g., proteases, thromboplastin, plasminogen activator, lymphokines, and complement, are not discussed here.

Histamine

One of the primary mediators of immediate hypersensitivity, histamine, is released mainly from pulmonary and other mast cells. The biochemical and cytological mechanisms of this release and pharma-
Peptides

It is not known that normal lung may contain or generate several active peptides (Said et al., 1980), including those discussed below.

Vasoactive Intestinal Peptide (VIP), a 28-residue neuropeptide occurring in the central and peripheral nervous systems, relaxes airway and pulmonary vascular smooth muscle, and induces systemic vasodilation, hypotension, and other effects (Said, 1980). In the lung, VIP is principally located in nerves supplying the airways and pulmonary vessels (Dey et al., 1981) as well as in mast cells (Cutz et al., 1978).

"Spasmogenic Lung Peptides" is a systemic vasodilator peptide that contracts airway, pulmonary vascular and other smooth muscle, and is distinct from other peptides with similar actions; it has been purified from normal lung tissue (Said and Mutt, 1977), but its chemical composition has yet to be determined.

Substance **P** which, like VIP, is mainly a neuropeptide with pulmonary localization in nerves to airways and pulmonary vessels (Dey and Said, 1981); it is a systemic vasodilator but contracts smooth muscle structures in the lung.

A Bombesin-like Peptide has been demonstrated in endocrine cells of fetal lungs (Wharton et al., 1978) but not yet in lungs of adult animals. Bombesin, a 14-residue peptide from the skin of the amphibian *Bombina bombina*, has spasmogenic properties on airway, pulmonary vascular, and other smooth muscle. The mammalian counterpart of bombesin is probably the 27-residue gastrin-releasing peptide (McDonald et al., 1979).

Bradykinin may be formed (and metabolized) in the lung, through the action of activated kallikrein on tissues kininogens. Bradykinin, a potent systemic vasodilator and vasodepressor, is capable of increasing systemic vascular permeability, but its ability, on its own, to increase pulmonary microvascular permeability has not been established. In combination with hypoxia, however, bradykinin can induce pulmonary edema (O'Brodovich et al., 1981).

Angiotensin II, generated through the action of angiotensin I-converting enzyme in pulmonary endothelium, constricts pulmonary as well as systemic vessels (Segel et al., 1960). A role for angiotensin II in the pulmonary vasoconstriction induced by hypoxia was once proposed (Berkov et al., 1974) but has not been confirmed. Inhibition of the conversion of angiotensin I to angiotensin II has been reported to reduce pulmonary arterial pressure and vascular resistance (Niarchos et al., 1979).

Lipids

Prostaglandins and Related Lipids. The initial triggering reaction for the biosynthesis of all prostaglandins and related lipids is the activation of phospholipase A₂, which releases free arachidonic acid from membrane phospholipids. A variety of potent compounds may be synthesized by the lung from arachidonic acid, and their biosynthesis follows one of two major pathways: one catalyzed by cyclo-oxygenase and the other by lipoxygenase enzymes (Fig. 4). Active biosynthetic products formed through the cyclo-oxygenase pathway include the intermediate endoperoxides, PGG₂ and PGH₂, the "primary" prostaglandins, PGE₂, PGF₂a, and PGD₂; thromboxane A₂; and prostacyclin (PGI₂). With the exception of PGI₂, all of these compounds are pulmonary vasoconstrictors with varying potencies. All but PGE₂ and PGI₂ are also bronchoconstrictors. There is not direct evidence, however, that any of these products can increase pulmonary vascular permeability. Thromboxane A₂ induces, and PGI₂ inhibits, platelet aggregation. The nature and relative preponderance of these biosynthetic products vary from species to species, (Al-Ubaidi and Bakhle, 1980).

The lipoxygenase system catalyzes the formation of several active compounds, including derivatives of hydroperoxy-eicosatetraenoic acid (HETE and HPETE), with chemotactic activity toward leukocytes, and the leukotrienes, of which leukotriene C₄ and D₄ have the activity of the "slow-reacting substance of anaphylaxis" (SRS-A), i.e., slow and prolonged contraction of airways and other smooth muscle (Kellaway and Trethewie, 1940; Dahlén et al., 1980). Stimulated pulmonary generation of arachidonic acid, and subsequent biosynthesis of products catalyzed by cyclooxygenase and by lipoxygenase, are known to occur in a number of experimental condi-

![Figure 4. Transformations of arachidonic acid in the lung (see text).](http://circres.ahajournals.org/)

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dothing.
tions that mimic physiological and pathophysiological states. Among these are: hyperventilation and respiratory alkalosis, pulmonary embolism, pulmonary edema, endotoxin and hemorrhagic shock, and instillation of HCl in the airways (Said, 1977, 1981; Cook et al., 1980; Aoyagi et al., 1981). The release of prostaglandins and other lipids in these states probably contributes to the pathogenesis of lung injury and to altered pulmonary and systemic function, but the precise contributions of each compound are still incompletely known. The leukotrienes (SRS-A) are also believed to be important mediators of immediate hypersensitivity.

The anti-inflammatory effects of corticosteroids are attributable, in part, to their ability to inhibit the formation of arachidonic acid, the principal precursor in this system, by inducing the synthesis of an inhibitory peptide (Flower and Blackwell, 1979).

"Platelet-Activating Factor" (PAF). The PAF factor, recently identified as acetyl glyceryl ether phospho-rylcholine (Hanahan, 1980), is released from sensitized rabbit basophils and human neutrophils. As well as inducing platelet activation, PAF has potent activities, including constriction of airway smooth muscle and the production of edema.

Relation of Metabolic Activities to Pulmonary Vascular Responses

The vasoactive hormones metabolized or generated by the lung are capable of influencing all aspects of pulmonary hemodynamics, including vascular smooth muscle tone, vascular pressures, blood flow, and microvascular permeability. Systemic arterial blood pressure and peripheral vascular resistance also may be affected.

The following are examples of the participation of vasoactive hormones and their pulmonary metabolism in physiological regulation:

1. Vasodilator prostaglandins (and prostacyclin) released during hyperventilation may promote increased pulmonary blood flow to match the augmented ventilation (Said et al., 1974a, 1977).

2. Vasoconstrictor prostaglandins and related compounds, still incompletely identified, may mediate the hypoxic vasoconstrictor response, at least in some species (Said et al., 1974a), whereas vasodilator compounds, particularly prostacyclin, may help modulate (or moderate) this response (Gerber et al., 1980; Y. Hamasaki, H.-H Tai, and S.I. Said, unpublished observations).

3. Prostacyclin, a potent inhibitor of platelet aggregation that is synthesized by endothelial cells (Wek-...
Dixon et al., 1979; Kaufman et al., 1980), that would contribute to the pathophysiological responses.

Concluding Comments

Within the past few years, the capacity of the lung for metabolic activity has been well documented. Examples are the selective and efficient removal of serotonin, bradykinin, and certain prostaglandins, the conversion of angiotensin I to angiotensin II, and the synthesis and release of a variety of prostaglandins, thromboxane, prostacyclin, leukotrienes, and a variety of peptides and enzymes. The potential implications of these pulmonary activities for the regulation of pulmonary and systemic vascular and airway smooth muscle, as well as platelet function, are considerable. Similarly, the consequences of impaired metabolism or excessive release could include pulmonary vasoconstriction, systemic hypotension, airway constriction, platelet aggregation, and increased pulmonary microvascular permeability. Firm conclusions on the full physiological and pathophysiological significance of these metabolic lung functions and of their alterations in disease must await much additional investigation.

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