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Metabolism of Vasoactive Hormones by Lung

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ALTHOUGH PRIMARILY involved in gas exchange, the lungs have important non-respiratory functions, including phagocytosis by alveolar macrophages, filtering of emboli and circulating leukocytes, biosynthesis of phospholipid for surfactant, and excretion of volatile substances.⁸⁵ Less widely appreciated but potentially equally important is the ability of lung to clear certain vasoactive hormones from pulmonary blood and to synthesize or activate others, which then enter blood leaving the pulmonary circulation. Thus, the lungs, ideally situated for such a purpose, can alter arterial blood concentrations of vasoactive hormones. The purpose of this article is to outline recent developments in our understanding of the ability of lung to affect concentrations of potent vasoactive hormones in circulating blood, and to direct attention to situations in which this ability may be altered.

Table 1 lists some of the hormones affected by passage through the pulmonary vasculature. In addition, table 1 indicates some of the now-impressive list of drugs which, after systemic administration, are concentrated or metabolized by lung. Many of these drugs and hormones are organic bases, but otherwise they lack common chemical characteristics. Their pharmacologic properties include vasoconstrictor, vasodilator, antihistamine, antidepressant, and psychotomimetic actions. Yet, despite the variety of drugs taken up by the lung, pulmonary metabolism of compounds such as hormones displays a high degree of selectivity. Bradykinin²¹ and 5-hydroxytryptamine (serotonin)^{1, 29, 60} are almost completely cleared from blood as they pass through the lung, while histamine^{12, 19} and epinephrine^{80, 87} pass through the pulmonary circulation essentially

unchanged. The precise structural specificity is illustrated by the fact that although norepinephrine is removed from pulmonary blood^{19, 80} and metabolized in the lung, N-methylnorepinephrine (epinephrine) passes through the lungs without loss.^{80, 87} Vane, whose work has contributed much to our knowledge in this area, has proposed⁶² an explanation for such selectivity. Whereas bradykinin and 5-hydroxytryptamine have predominantly local actions and are normally prevented from reaching the arterial circulation, a compound such as epinephrine is a circulating hormone and therefore should pass through the lungs without loss.

Some of the details of pulmonary metabolism are known well enough to merit individual discussion of several important compounds. In some cases it is possible also to speculate on the significance of pulmonary metabolism.

5-Hydroxytryptamine

Inactivation of 5-hydroxytryptamine by lung has been confirmed by several groups^{1, 17, 19, 29, 60} following the initial demonstration by Gaddum and his collaborators²⁴ in 1953. Between 30 and 40 per cent of a single dose and as much as 92 per cent of the amount of 5-hydroxytryptamine infused systemically are removed during one passage through dog⁶⁰ or rat¹ lung. A recent study in this department²⁷ revealed that 65 per cent of radioactive 5-hydroxytryptamine injected intravenously as a bolus was removed by the lungs in anesthetized patients. Although the fate of this amine in the lungs of man is unknown, following its removal by animal lung, 5-hydroxytryptamine is deaminated by intrapulmonary monoamine oxidase.^{1, 29} Inhibition of this enzyme results in preservation of intrapulmonary 5-hydroxytryptamine.^{1, 29} However, monoamine oxidase inhibition does not alter the magnitude of pulmonary 5-hydroxytryptamine removal.^{1, 29}

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TABLE 1. Effects of Passage through the Lung on Various Substances

	Selected References
Substances inactivated (bound and/or metabolized) by the intact lung	
Hormones	
5-Hydroxytryptamine	1, 24, 27, 29, 33, 60
Acetylcholine	19
Norepinephrine	19, 27, 30, 37
Bradykinin	21
Prostaglandins E ₁ , E ₂ , F _{2α}	22
Drugs	
Chlorpromazine	23, 56
Lysergic acid diethylamine (LSD)	5
Δ-9-Tetrahydrocannabinol	42
Imipramine, desmethylinipramine	54
Nortriptyline	65
Mepacrine	15
Propranolol	34
Sulfanilamide	54
Cyclizine, chlorcyclizine	40
Tripelennamine	64
Diphenhydramine	31
Substances activated or synthesized by the lung	
Angiotensin I (converted to angiotensin II)	11, 36, 45
Prostaglandins E ₁ and E ₂	43, 49, 50
Substances unaffected by passage through the lung	
Angiotensin II	11, 36, 45
Epinephrine	30, 37
Dopamine (dihydroxyphenylalanine)	13
Eledoisin	21
Isoproterenol	12
Prostaglandins A ₁ and A ₂	22, 44
Histamine	12, 19

indicating that the primary process involved is uptake rather than enzymatic degradation. It is likely that additional enzymes are also involved in degrading 5-hydroxytryptamine within lung. Gillis and Iwasawa observed²⁹ that the amine content of lungs perfused with 5-hydroxytryptamine in the presence of monoamine oxidase inhibitor was only 60–70 per cent of that calculated to have been removed. Axelrod⁴ reported enzymatic N-methylation of 5-hydroxytryptamine by rabbit lung. Perhaps this metabolic route is available for the disposition of exogenous 5-hydroxytryptamine removed by lung.

More than 80 per cent of 5-hydroxytryptamine-¹⁴C taken up by rat lung is metabolically degraded,²⁰ and relatively little is bound unchanged.^{1, 20} However, the small portion that remains unchanged is apparently firmly

bound to lung and can be detected as long as one week after its administration.⁶ One site of 5-hydroxytryptamine binding may be Type II alveolar epithelial (septa) cells.²⁵

Pulmonary uptake of 5-hydroxytryptamine may have clinical significance in several ways. Gruby *et al.*³³ postulated that derangement of pulmonary 5-hydroxytryptamine removal may permit plasma concentrations of this amine to increase to the point where platelet aggregation is promoted. This effect is known to occur at 5-hydroxytryptamine levels roughly ten times normal.⁷ In this manner, depression of the 5-hydroxytryptamine removal mechanism may be associated with a tendency toward venous thrombosis.

How might such malfunction of 5-hydroxytryptamine uptake be produced? One likely mechanism is deliberate "short-circuiting" of the

pulmonary vascular bed during cardiopulmonary bypass. This procedure can be expected to permit abnormally high circulating levels not only of 5-hydroxytryptamine, but also of bradykinin and of other substances normally restricted to the venous circulation. Surprisingly, we recently found²⁷ that immediately after heart-lung bypass in patients with normal pulmonary arterial pressure, pulmonary extraction of both 5-hydroxytryptamine and norepinephrine were significantly greater than before bypass. The reason for this occurrence is unknown. If the effect persists into the postoperative period, it could decrease pressor responses to intravenous infusions of norepinephrine because of unexpectedly efficient pulmonary clearance of the amine.

In another study (Gillis *et al.*, unpublished observations), it was found that in patients with pulmonary hypertension, 5-hydroxytryptamine and norepinephrine extraction was significantly elevated. Extraction decreased after heart-lung bypass to levels similar to those seen following bypass in the first group of patients studied. Thus, it appears that hemodynamic or pathologic changes associated with pulmonary hypertension may be reflected in altered extraction of norepinephrine or 5-hydroxytryptamine by lung.

Tricyclic antidepressants are effective inhibitors of 5-hydroxytryptamine as well as norepinephrine uptake^{1, 29, 37} in lung and peripheral tissues. It is possible that in patients with high enough blood levels of these drugs, or other drugs that might inhibit lung uptake of vasoactive substances, both norepinephrine and 5-hydroxytryptamine may reach the arterial circulation in unusually high concentrations. The antihistamine drug tripeleennamine³⁹ and the tricyclic antidepressants imipramine and desmethylinipramine potentiate the pressor effects of norepinephrine and also inhibit uptake of this amine by lung (Gillis and Iwasawa, unpublished observations). These drugs are avidly taken up by lung^{54, 64} and, being organic bases, may inhibit pulmonary uptake of norepinephrine or 5-hydroxytryptamine by competing with the amines for binding sites,⁶² possibly in capillary endothelial cell membranes.

Removal of 5-hydroxytryptamine by lung has been linked to the fact that right-sided heart-valve lesions predominate in patients with intestinal carcinoid tumors and wide-

spread metastases.³² The same argument could presumably be advanced to implicate bradykinin (or other kinins), since it, too, is produced in the carcinoid syndrome^{20, 45} and is almost totally inactivated during passage through lung.²¹

Norepinephrine

Removal of norepinephrine by lungs of several species, including man, has been reported.^{29, 30, 37} About 20 per cent of norepinephrine infusions are removed by cat or dog lung,³⁰ while lungs of anesthetized patients remove about 25 per cent of a single intravenous injection in one circulation.²⁷

Its immediate biosynthetic precursor, dopamine, passes through the pulmonary circulation essentially without loss,¹³ again emphasizing the specificity of uptake by lung. Pulmonary removal of norepinephrine is reduced by a number of drugs, among which phenoxybenzamine and cocaine are the most potent.^{28, 38} The sites of both norepinephrine and 5-hydroxytryptamine uptake by lung are unrelated to adrenergic innervation, since destruction of sympathetic nerve endings⁵⁹ by 6-hydroxydopamine pretreatment fails to affect uptake of either amine (Gillis and Iwasawa, unpublished data). However, the site of norepinephrine uptake is distinct from that responsible for 5-hydroxytryptamine uptake, since neither amine influences pulmonary uptake of the other.¹ Also, it is possible by pharmacologic means to block uptake of norepinephrine selectively while 5-hydroxytryptamine uptake remains intact, and vice versa (Gillis and Iwasawa, unpublished observations).

If intrapulmonary metabolism of norepinephrine is prevented, the amine is found, by autoradiography³⁷ and fluorescence microscopy, to be localized in endothelial cells of capillaries and postcapillary venules.³⁸ Hypothermia (6 C) completely prevents norepinephrine binding at these sites.³⁸

Reducing the temperature of the medium perfusing lung *in vitro* to 6 C has been found in this laboratory to reduce norepinephrine uptake to 20 per cent of normal.³⁸ The Q_{10} for norepinephrine uptake by lung (between 25 C and 35 C) is about 3,³⁸ indicating a highly temperature-dependent process. 5-hydroxytryptamine uptake is also markedly im-

paired by hypothermia.^{38, 38} This fact may be important clinically, since hypothermia during surgery may permit unusually high concentrations of 5-hydroxytryptamine and norepinephrine to reach the arterial circulation.

Bradykinin

Bradykinin, a potent vasodepressor kinin, is formed in blood by the action of a proteolytic enzyme, kallikrein (kininogenase) on kininogen, an α_2 -globulin of plasma. Activation and release of bradykinin occur in a variety of conditions, including pulmonary edema, anaphylaxis and endotoxin and hemorrhagic shock.²⁰ The paroxysmal flushing seen in carcinoid syndrome is associated with increased blood concentrations of bradykinin.^{45, 46}

The lungs efficiently remove bradykinin from the pulmonary circulation. Ferreira and Vane²¹ reported 80 per cent inactivation of this peptide in cats, an observation confirmed by Biron in the rat.¹⁰ In contrast to 5-hydroxytryptamine, inactivation of bradykinin seems to be primarily enzymatic. Ryan *et al.*⁵⁴ found that although lungs perfused with radioactive bradykinin fail to bind significant amounts of radioactivity, the pulmonary venous effluent lacks the biological activity of the peptide. The enzyme(s) involved in degradation is unknown but differs from that present in blood or kidney.²⁰

Prostaglandins

Prostaglandins, a group of lipids with an enormous range of potent biological actions, are widely distributed throughout the body. Particularly high concentrations are found in seminal fluid,⁹ and prostaglandins are now known to be released from many tissues, including spleen,^{18, 22} adrenal glands,⁵² and stomach,⁸ following neural stimulation. Prostaglandins are also released from previously sensitized guinea pig lung challenged with egg albumin,^{48, 50} by pulmonary emboli,⁴³ and even by gentle manipulation of the lung.^{48, 50} The lungs contain relatively small amounts of endogenous prostaglandins,⁵² and stimulation by these procedures causes release of more prostaglandins than they originally contained. Such release, therefore, indicates synthesis of prostaglandin within the lung.⁴⁸ Cat, dog, and rabbit lungs²² permit free passage of prostaglandins A_1 and A_2 in blood but remove

more than 90 per cent of infused prostaglandins E_1 and E_2 and $F_{2\alpha}$. McGiff *et al.*⁴⁴ suggested that since prostaglandins A_1 and A_2 pass freely through lung, they function as true circulating hormones, while prostaglandins of the E series are to be considered local hormones and restricted, therefore, to the venous circulation. Anggard and Samuelson⁸ demonstrated the existence in lung of an enzyme which metabolizes prostaglandins to a variety of products, suggesting that pulmonary removal may be primarily enzymatic, a proposal subsequently supported by Piper *et al.*⁵⁰

Prostaglandin E_2 is a potent vasodilator substance which is released during the anaphylactic response^{40, 50, 63} and may contribute to the hypotension characteristic of this condition. Piper and Vane⁵⁰ recently suggested that since prostaglandin E_2 is released in proportion to the degree of inflation of the lung, those areas of lung that are well expanded may release more prostaglandin E_2 , thus dilating adjacent pulmonary vessels and insuring greater blood flow to those areas. In this way, prostaglandins synthesized *de novo* may qualify for a role of regulating intrapulmonary blood flow.⁵⁰

A recent hypothesis⁵⁸ attempts to link pulmonary release of prostaglandin E_1 to production of migraine headache. Intravenously administered prostaglandin E_1 causes headache. Occasionally, very high venous blood concentrations of prostaglandin E_1 have been reported in some patients with carcinoid disease who have headache along with the characteristic flush. Sandler and his colleagues⁵⁸ therefore suggested that prostaglandins may be involved in migraine. It was difficult, however, to detect increased prostaglandin concentrations in venous blood of patients with migraine. After it was reported² that 5-hydroxytryptamine released prostaglandins from the lung *in vitro*, Sandler⁵⁸ suggested that this action may occur also in man. Thus, 5-hydroxytryptamine or some other circulating amine may release prostaglandins into arterial blood, where they cause migraine headache. In support of this idea, Sandler notes that methysergide, which is effective in the treatment of some cases of migraine, blocks the prostaglandin-releasing action of 5-hydroxytryptamine in lung.² Although this is a provocative hypothesis, it remains to be established experimentally, and it

would fail to explain the unilateral headache which characterizes many cases of migraine.

Vasoactive Peptides

The lung provided the answer to a puzzling feature of the pharmacology of the vasoactive peptides, angiotensin I and angiotensin II. Angiotensin I is a decapeptide formed by the action of the enzyme renin on a plasma alpha₂-globulin. The octapeptide angiotensin II is formed from angiotensin I by loss of the C-terminal histidyl-leucine moiety. Angiotensin I has less than one tenth of the vascular smooth muscle-stimulating activity of angiotensin II,¹⁴ yet angiotensin I causes as rapid and as large an increase in blood pressure after its intravenous injection as does angiotensin II. This was formerly thought to result from rapid conversion of the decapeptide to angiotensin II in blood. However, it has since been found⁴⁵ that lung rather than blood is the site of this conversion and that, although it can occur in blood, the process is too slow to account for the virtually immediate pressor response to intravenously injected angiotensin I. Ng and Vane⁴⁵ estimated that 80 per cent of infusions of angiotensin I were converted to angiotensin II by lung. As might be expected if angiotensin II is the biologically active entity, this octapeptide passes through dog³⁸ and rat⁴¹ lung without loss. In patients undergoing diagnostic cardiac catheterization, it was found¹¹ that the aortic pressor response to angiotensin I injected at the pulmonary artery is much greater than that seen in response to similar doses injected at the ascending aorta, implying intrapulmonary conversion of angiotensin I to angiotensin II by human lung. It was also noted¹¹ that in man, as in other species,^{38, 41} angiotensin II passes through the lung without alteration. Thus, lung probably functions as the main site for production of angiotensin II, the most potent pressor substance elaborated by the body. Conversion of angiotensin I to angiotensin II probably occurs in the capillary endothelium of lung, where it has been suggested that the particulate bound "converting" enzyme of lung homogenates originates.⁵⁷ Taken with the localization of bound norepinephrine in the same histologic site (see above), this fact indicates that capillary endothelium is important in the binding and metabolism of at least some vasoactive hormones.

Microsomal Enzymes in the Lung

In addition to its ability to regulate arterial blood concentrations of many potent vasoactive substances, the lung is known to have a microsomal drug-metabolizing system (mixed-function oxidase)⁴⁸ qualitatively similar to that in liver. Halothane and methoxyflurane undergo mixed-function oxidase-dependent reactions in liver,¹⁶ and it is reasonable to regard lung also as a potential site for such action. A recent study⁶¹ established the presence of nonvolatile halothane metabolites in lung after inhalation of the anesthetic. Although these metabolites may have been formed elsewhere and transported to the lung, the observation⁶¹ is nevertheless compatible with intrapulmonary metabolism of halothane.

Significance of Pulmonary Metabolism of Vasoactive Hormones

Although there is abundant evidence establishing the lung as an organ capable of synthesizing, binding, and metabolizing vasoactive hormones, the physiologic significance of these processes is uncertain. Equally unclear is whether derangement of one or more of these functions is related to pulmonary disease processes. Certainly, however, it is clear that each hormone listed in table 1 has profound effects on the smooth muscle tone of pulmonary and systemic vascular beds and of critical nonvascular sites such as the airway and the gastrointestinal tract. By inactivating some hormones and synthesizing others, the lung can significantly change the arterial blood concentrations of these substances, compared with those in venous blood. Thus, measurements of vasoactive hormone content of venous blood may not accurately reflect the concentrations in arterial blood.⁶² The arterial concentration may be physiologically more meaningful, when one is considering arteriolar tonus and systemic effects.

Merely to prove that the lung removes, metabolizes, or synthesizes certain drugs and vasoactive hormones does not establish the significance of these processes in cardiopulmonary physiology or pathophysiology. However, an analogy might be drawn with the initial observations of high dopamine concentrations in the basal ganglia. These observations led ultimately to linking the extrapyramidal symptoms of parkinsonism to reduced concentrations of

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dopamine. Still later came the effective use of the dopamine precursor, *l*-dopa, in treatment of some cases of the disease. At present we know only that the lung has the metabolic functions described above; their roles remain to be elucidated. The evidence even at this stage is nevertheless sufficiently persuasive to suggest that anesthesiologists should be alert to these properties of lung and to the potential for their disruption or derangement by drugs, especially those administered via the lung. This view is strengthened by our recent observation that halothane or nitrous oxide significantly reduced norepinephrine uptake by perfused lungs.⁶⁶

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