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COMMENTARY

PULMONARY DISPOSITION OF CIRCULATING VASOACTIVE HORMONES*

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The lung metabolizes a wide variety of substances including environmental pollutants [1], steroid hormones [2, 3] and psychotomimetic drugs [4, 5]. Recently, there has been increasing awareness of the role played by these processes in regulating systemic arterial blood levels of important vasoactive hormones, including prostaglandins, peptides and biogenic amines [6–12]. Such regulation is achieved by uptake and catabolism of substances reaching lung via the pulmonary artery (e.g. prostaglandins of the E and F series, serotonin and bradykinin) or by *de novo* synthesis within lung (e.g. angiotensin II and prostaglandins). In either case, the vasoactive hormone content of pulmonary venous blood can differ greatly from that of the pulmonary arterial inflow. There is considerable potential for drug-induced modification of these non-ventilatory functions of lung; this is strikingly illustrated by considering that all medication administered by the intravenous route proceeds directly to the lung. Our prime purpose in this paper is, therefore, to focus attention on recent data concerning inactivation of vasoactive hormones by lung and on circumstances in which it is altered.

It is appropriate first to emphasize that since the pulmonary circulation is interposed between the right and left heart (and therefore receives the entire cardiac output), the total circulating blood volume passes through the lungs several times a minute. Secondly, within the pulmonary vasculature, blood or perfusion medium is exposed to a huge capillary endothelial surface (70 square meters, or about 750 square feet, in man [8, 9] across which movement of vasoactive hormones and their metabolites can occur. Thus, the lung circulation can function as a highly efficient "biochemical filtration system" and in this respect can be as effective as the liver. For example, if we assume 30 per cent metabolic degradation of compound A in the pulmonary circulation and a cardiac output of 5 liters/min, then blood reaching the lungs will be cleared of A at a rate of (5 × 0.3) or 1.5 liters/min. Even if the same substance is totally metabolized by liver (with resting blood flow of about 1.6 liters/min), the clearance is only 1.6 liters/min.

The term removal is used throughout this paper to connote a net reduction in concentration of vasoactive hormone in lung effluent when compared to that in pulmonary arterial inflow. Removal probably reflects transport and metabolic inactivation of hormone. Inactivation refers exclusively to metabolic change(s) resulting in formation of a physiologically less active product.

AMINES

The biogenic amines, 5-hydroxytryptamine (5-HT) and norepinephrine (NE), are removed on passage through lungs of all species studied thus far, including dog [13–15], cat [15, 16], rat [17–20], guinea pig [21], calf [22], pony [22] and rabbit [23]. During a single pass through the pulmonary circulation, both compounds are rapidly and extensively degraded by monoamine oxidase (MAO) and, in the case of NE, also by catechol-*O*-methyl transferase, to their corresponding deaminated and/or *O*-methylated products [17–20, 23]. After short periods of perfusion with radioactively labeled 5-HT or NE, most of the radioactivity found in lung tissue was in the form of these metabolites [17, 19, 20]. Recently, pulmonary removal of both 5-HT and NE was also demonstrated to occur in lungs of anesthetized patients undergoing cardiac revascularization [24, 25] as well as in those of healthy, conscious subjects [26].

For both 5-HT and NE, the rate-limiting step in removal appears to be transport into the pulmonary vasculature [17–21, 23]. In the absence of degradation within lung, equilibrium between entry and exit rates would eventually be reached, for neither amine is normally bound in lung; net removal would then be zero. Since there is substantial net removal of NE and 5-HT, it must, therefore, reflect, primarily, metabolic degradation of both substances in the pulmonary vascular bed. The rapid appearance of deaminated metabolites in effluent from lungs perfused *in vitro* with 5-HT or NE suggests that uptake and inactivation of circulating amines likely occur at or near the vascular surface. The primary morphologic sites for removal of both NE and 5-HT are capillary and small vessel endothelial cells [17, 20, 27, 28]. Detection of accumulated amines in these cells by fluorescence histochemistry [28] or autoradiography [17, 20, 27] is possible only when NE or 5-HT is perfused along with inhibitors of their intrapulmonary metabolism. Therefore, it is likely that the enzymes responsible

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for 5-HT and NE inactivation are probably also associated with these cells. Histochemical studies have previously suggested the presence of monoamine oxidase in pulmonary endothelium [29].

Transport of 5-HT and NE is, at least in part, energy and sodium dependent. Removal of both amines is greatly reduced when lungs are perfused under hypothermic conditions (6°) [19, 20, 28]. Removal of 5-HT and NE is saturable at 37°, but is linearly related to amine concentration when perfusion is carried out at 6° [19, 20, 28]. Apparent K_m values for the saturable components of NE and 5-HT transport are between 1 and 2 μM [30]. Similar values were reported [17, 19, 20, 28] even when the passive (i.e. temperature-insensitive) component for removal is included in the calculations. A detailed kinetic analysis of the overall removal process for 5-HT and NE in rabbit lung is available [30].

Pulmonary removal of both 5-HT and NE is also diminished by many drugs [10, 31], including ouabain [19, 20, 28] and by low sodium or high potassium [19, 20] in the perfusion medium. Anoxia slightly reduces removal of both amines [19, 28] whereas iodoacetate, an inhibitor of the Na^+-K^+-dependent ATPase, significantly reduces NE removal [28]. Therefore, the mechanism of this process in lung may involve a sodium-dependent carrier-mediated transport [19, 20, 28]. Halothane and nitrous oxide reduce NE removal in perfused rabbit [32] and dog [33] lung, perhaps by inhibiting such a process in endothelial cell membranes [7, 31].

The sites for 5-HT and NE transport on the endothelial cell membrane appear to be functionally distinct, since each amine only weakly inhibits transport of the other [19, 20, 34]. The existence of separate sites for transport is also supported by the observation that 5-HT can protect its own site from irreversible inhibition by phenoxybenzamine, while leaving functionally intact that for NE [34]. In similar experiments, it was established that NE protects only its own transport site.*

Pulmonary removal of NE has characteristics in common with both neuronal and extraneuronal uptake of this catecholamine [31]. The pulmonary process resembles adrenergic neuronal uptake in that cocaine and the tricyclic antidepressant drugs, imipramine and amitriptyline, inhibit NE uptake [17, 20, 23, 31, 34]. Yet, pretreatment of rabbits with 6-hydroxydopamine does not alter the magnitude of NE removal [34]. Also, normetanephrine effectively inhibits removal of this amine by perfused rabbit lung whereas the β-blocking agent, propranolol, was ineffective [20, 34]. The latter observations are consistent with characteristics of the extraneuronal uptake process. As might be anticipated, therefore, NE removal by lung lacks stereospecificity [28]. Also, 17-β-estradiol, which markedly reduces extraneuronal accumulation of NE by heart [35], is the most effective steroid inhibitor of NE removal by rabbit lung [31].

The capacity of lung to remove and inactivate other compounds structurally related to 5-HT and NE has received relatively little attention. Amphetamine [36, 37], phenylethylamine (PEA) [37] and metaraminol [38] are removed on passage through the pulmonary vasculature, whereas the structural analog, dopamine, has been reported by several investigators to be unaffected by passage through rat [20] and dog lung [39]. Unpublished observations from our laboratory reveal, in contrast, that dopamine is extensively removed and deaminated on a single pass through rabbit lung; no NE formation is seen. We also find that perfused rabbit lung removes and deaminates tyramine, octopamine and the structurally related psychotomimetic agent, mescaline. Though these results suggest an apparent lack of specificity for transport of amines in lung, it is known that epinephrine largely escapes degradation during perfusion through dog [15], rabbit [23], rat [17] and human [40] lungs. Similarly, histamine [13, 41], imidazole [42] and isoproterenol [23, 41] are unaffected by transpulmonary passage. Although histamine escapes degradation by perfused lung, it is extensively metabolized by minced preparations of guinea pig [43], rat [43], cat [44] and human lung [45]. These data point to the importance of using perfused lungs in order to determine the fate of circulating vasoactive substances (see also Ref. 6).

The primary pathway for pulmonary inactivation of amines is deamination by the enzyme MAO. We recently found [37] that three functional forms of MAO exist in the intact perfused rabbit lung. Substrate and inhibitor studies indicated that two of these forms resemble the A and B forms of the mitochondrial oxidase. The pulmonary form of MAO which deaminates 5-HT, and which is most sensitive to inhibition by the alkaloid, harmaline, resembles the type A mitochondrial oxidase whereas the other form, which oxidizes PEA and is relatively insensitive to harmaline, is analagous to the B form of MAO. Thus, experiments with perfused lung represent the first demonstration that functionally distinct forms of the mitochondrial oxidase exist in an intact organ and, therefore, may well exist *in vivo*. In confirmation of our findings, Bakhle and Youdim [46] reported evidence for the B form of MAO in perfused rat lungs. The third form of the pulmonary oxidase found in the perfused rabbit lung deaminates PEA and is inhibited by the carbonyl reagent, semicarbazide [37]. The properties of this enzyme resemble those of the oxidase present in plasma and several large arteries. Unpublished observations† from our laboratory reveal that this form of the oxidase is solely responsible for deamination of mescaline in the perfused rabbit lung.

It was recently pointed out [31, 34] that certain properties of pulmonary removal of circulating amines resemble aspects of brain endothelial disposition of amines. For example, it has been reported that endothelial MAO deaminates dopamine and NE in brain vasculature and thus may act to prevent amine transport into brain [47, 48]. As mentioned above, the endothelium of lung vasculature likewise contains MAO which rapidly and extensively deaminates [37] 5-HT, NE, dopamine and other structurally related compounds. Fluorescence histochemical visualization of 5-HT and NE in the endothelium of perfused lungs is possible only when MAO was

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inhibited [28]. Similarly, dopamine fluorescence in brain capillaries was observed only when animals were pretreated with an MAO inhibitor [47]. If future experiments should offer additional evidence of the resemblance between lung and brain endothelial function, the perfused lung might profitably be viewed as a reasonable model for the study of brain endothelial function in relation to amine disposition.

VASOACTIVE PEPTIDES

Ng and Vane [49] proposed, and it has been confirmed by many other groups, that extensive conversion of angiotensin I (AI) to angiotensin II (AII) occurs within the pulmonary circulation. Approximately 80 per cent conversion takes place on a single passage through the dog lung, while little or no conversion occurs elsewhere in the body [49, 50]. Hydrolysis of AI to its active form by angiotensin converting enzyme also occurs in perfused guinea pig [51], rat [51–54], cat [51] and sheep [55] lungs. Converting enzyme is found not only in lung but also in aorta, carotid and other arteries [56] and, therefore, may be associated with all blood vessels. As a consequence of the extensive pulmonary vascular surface, conversion of the decapeptide to AII is expected to be relatively greater in lung than in other organs [56].

Unlike the parent peptide, AII escapes hydrolysis in the pulmonary circulation of dogs [51, 57], guinea pigs [51], cats [51] and rats [51, 53]. However, during a single passage through dog kidney and liver, approximately 62 and 75 per cent of the AII activity, respectively, is lost [57]. Rapid inactivation of formed AII in these organs may account, at least in part, for the apparent absence of converting enzyme activity observed during perfusion with AI.

The ability of the lung vasculature to hydrolyze the decapeptide AI is not unique. Bradykinin also is rapidly and extensively inactivated within the pulmonary circulation of cat [58], dog [59], rat [59, 60], sheep [55] and guinea pig [59]. In these species, more than 80 per cent of the activity of bradykinin disappeared during a single passage through the lung. Though a number of hydrolytic enzymes are capable of degrading bradykinin [59–61], the enzyme, bradykininase, responsible for the initial inactivation of this hormone in perfused lung, has been characterized as a dipeptidyl-carboxypeptidase [59, 62].

Several investigators have shown that mean pulmonary transit time for the hydrolytic products derived from either AI or bradykinin in perfused lung preparations was identical to that of an intravascular marker [63]. Accordingly, it was suggested that the angiotensin converting enzyme and bradykininase were likely to be associated with the luminal surface of the endothelial lining of pulmonary vessels. In blood-perfused dog lung *in vitro*, the extent of AI conversion to AII increased with increasing pulmonary vascular surface area and mean transit time [64]. Using endothelial cells isolated on cellulose nitrate paper strips, Smith and Ryan [63] demonstrated that bovine pulmonary arterial endothelium converts AI to AII. They also found that plasma membrane fractions isolated from rat lung homogenates hydrolyze both AI and bradykinin. On the basis of these experiments and autoradiographic studies, they suggested that these enzymes are localized within the *caveolae* of the pulmonary endothelial membranes [63]. In recent experiments using an immunological technique to locate AI converting enzyme on endothelial membranes, Ryan *et al.* [65] found this enzyme to be associated primarily with the luminal surface of capillary and venule endothelium. Converting enzyme was also detected on the outer membrane of pulmonary endothelial cells grown in culture [66].

Much of the literature dealing with pulmonary metabolism of AI and bradykinin has concerned attempts to establish whether hydrolytic cleavage of histidyl-leucine from AI and of phenylalanyl-arginine from bradykinin, are carried out by the same dipeptidyl-carboxypeptidase [50]. Most of the evidence accumulated from experiments with perfused lung preparations and with purified or partially purified preparations of these enzymes is consistent with the view that hydrolysis of both peptides occurs on the same enzyme. Studies from several laboratories indicate that the activities of both enzymes in the perfused lung are inhibited by a variety of substances including EDTA [54, 62], 2,3-dimercaptopropanol, *N*-ethylmaleimide [62] and a variety of venom peptides isolated from the Brazilian pit viper, *Bathrops jararaca* [67–69]. In addition, bradykinin is also a potent inhibitor of angiotensin I conversion in perfused rat lung [54]. Other studies, using partially purified preparations of converting enzyme and bradykininase, have demonstrated that each peptide inhibits hydrolysis of the other [61, 68]. Highly purified converting enzyme from rabbit lung microsomes has a molecular weight of approximately 140,000 and also hydrolyzes phenylalanyl-arginine and seryl-proline from bradykinin [70].

Considerable attention has been focused on the fact that Cl^- is essential for converting enzyme activity, *in vitro*, but not for bradykinin inactivation [62, 68]. This observation suggests that AI and bradykinin hydrolysis may result from the action of different dipeptidases. However, Cushman and Cheung [69] found that Cl^- activation of a purified preparation of rabbit lung converting enzyme depended on the structure of the peptide used to assay enzyme activity. With a series of synthetic peptides, these investigators found that Cl^- had a range of effects on the converting enzyme and in one case even inhibited the enzyme. Accordingly, they suggested that Cl^- acts as an allosteric modifier of the converting enzyme.

The synthetic peptides used by Cushman and Cheung [69] also act as competitive inhibitors of AI conversion. It is interesting to note that one such compound, the synthetic nonapeptide, SQ 20881, antagonizes the pressor response to angiotensin in man [71] and significantly decreased the mean diastolic pressure in 12 of 13 hypertensive patients [72]. Accordingly, it was suggested that this peptide may be effective in the treatment of some forms of human hypertension.

In light of the role the renin-angiotensin system may play in hypertension and the potential involvement of lung in this disease [72], it is somewhat surprising to find that conversion of AI to AII has not been demonstrated directly to occur in human lung vasculature [24]. Biron *et al.* [72, 74] reported an in-

crease in pressor response of conscious subjects when pulmonary arterial administration of AI was composed with intra-aortic administration. They interpreted their data as indicating pulmonary conversion of AI to AII even though the increase in response ranged from 0 to approximately 40 per cent. Demonstration of increased AII concentration in human left atrial blood after intravenous injection of AI seems necessary in order to answer this question definitively (cf. Ref. 24).

Overturf *et al.* [75] recently isolated and partially purified a dipeptidase from lung homogenates which could hydrolyze the parent decapeptide to AII. Of three converting enzyme preparations investigated, two also hydrolyzed bradykinin while the third was free of significant bradykininase activity. Overturf *et al.* [75] concluded that these two enzymatic activities in human lung are probably associated with separate enzymes. However, before acceptance of the proposal that separate enzymes hydrolyze bradykinin and AI in human lung vasculature, it must be established that the dipeptidase isolated [75] was associated with the endothelial membrane and not other cellular or subcellular components of lung.

PROSTAGLANDINS

Several investigations during the last decade revealed significant reduction in biological activity of prostaglandins* during their passage through the circulation of the intact lung. For example, PGE_1 is a more effective vasodepressor in rat [76], dog [77] and sheep [78] when administered by intra-arterial injection than when given intravenously, implying inactivation (uptake and/or metabolism) of the compound during transpulmonary passage. The first direct study of pulmonary inactivation was carried out by Ferreira and Vane [79] who found that 90% of the activity of intravenously injected PGE_1, PGE_2 or $PGF_{2\alpha}$ was lost in the pulmonary circulation. More recently Robertson [80] reported that only about half of the endogenous immunoreactive PGE_1 measured in right ventricular blood subsequently appeared in the aorta, thus establishing the existence, normally, of a gradient of PGE_1 across the lung circulation. Termination of physiological actions of prostaglandins might reflect uptake and retention as well as metabolism. Since little retention of the prostaglandins occurs [81, 82], such decreased activity likely reflects degradation to inactive metabolites.

Homogenates or cell-free preparations of lung metabolize prostaglandins of the E, F and A series first by oxidation of the secondary alcohol group at C-15 to form the corresponding 15-keto-prostaglandin [83–85]. This reaction is reversible and is catalyzed by the NAD-dependent 15-hydroxy-prostaglandin dehydrogenase (PGDH), an enzyme found in high concentration in lungs of various laboratory species and man [84, 86]. Subsequently, 15-keto-prostaglandins are converted to 13,14-dihydro-15-keto compounds by the NADPH-dependent [87], soluble enzyme Δ^{13}-prostaglandin-reductase [86]. Beta-oxidation of prostaglandins to the corresponding C-16 and C-18 homologues also occurs in lung homogenates [88].

Passage of [^{14}C]PGE_1 through blood-perfused cat lung results in its extensive conversion to 15-keto-13,14-dihydro-PGE_1 [89]. Metabolic degradation is primarily a function of lung cells rather than blood, for guinea pig [81] and rabbit [90] lungs perfused *in vitro* with Krebs solution also metabolize PGE_2 and PGE_1, respectively, to the corresponding 15-keto-13,14-dihydro derivatives. The apparent K_m and V_{max} for PGE_1 (metabolism or removal) in perfused rabbit lung [82] were 9 μM and 88 nmoles/lung $\times$ min^{-1}, respectively; interestingly, this K_m value is close to that reported [83] for PGE_1 metabolism by lung homogenates (7.7 μM).

Within the last year it was reported that PGE_1 [91] and $PGF_{2\alpha}$ [92], given by intravenous infusion, are removed to the extent of 68 and 77 per cent, respectively, during transpulmonary passage in conscious patients undergoing cardiac catheterization. It is unclear whether removal in these cases reflected uptake or metabolism. Studies in this laboratory [24] reveal that over 80 per cent of injected PGE_1 is metabolized during a single transit through the pulmonary circulation of anesthetized patients. Furthermore, we found that the metabolite appearing in left atrial blood of these patients is less polar than PGE_1 and seems to have the same chromatographic mobility as marker 15-keto-PGE_1.

In distinct contrast to prostaglandins of the E and F series, PGA_1 and PGA_2 survive passage through blood-perfused cat [93], dog [94] and human† [91] lungs. The fact that PGA compounds bind preferentially to plasma protein was suggested [95, 96] as an explanation for this observation; however, this proposal is difficult to reconcile with the greater than 50 per cent removal in human kidney *in situ* [91]. Earlier observations [93, 94] were made using bioassay techniques which, of course, could detect only disappearance of biological activity of a given prostaglandin. Possibly, PGA compounds are converted in blood-perfused lungs to metabolites that have similar biological activity on the assay organs as do the parent compounds. In support of this notion it was reported [97] that, while 15-keto-PGA_1 has much less vasodepressor activity than PGA_1, the 13,14-dihydro-PGA_1 and PGA_1 itself were equiactive in this respect. Also, Gross and Gillis [82, 98] found that [^{3}H]PGA_1 is converted to a chromatographically less polar metabolite during a single transit through rabbit lungs. Therefore, it seems appropriate to emphasize that, while "PGA_1-like" activity is unaffected by passage through the blood-perfused lung, some metabolic degradation of PGA_1 may occur, especially in experiments where Krebs medium rather than blood is used as the perfusion solution.

As much as 35–40 per cent of total tritium in rabbit lung effluent after 10 min of perfusion with [^{3}H]PGA_1 is not extracted into ethyl acetate [82, 98]. Polar conjugates of the cyclopentenone moiety of PGA_1 with reduced glutathione (GSH) or other compounds containing sulfhydryl groups have been reported [99, 100]. Formation of the GSH adduct can

*Abbreviations used are: PGE_1, prostaglandin E_1; PGE_2, prostaglandin E_2; PGA_1, prostaglandin A_1; PGA_2, prostaglandin A_2; $PGF_{1\alpha}$, prostaglandin $F_{1\alpha}$ and $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$.

†C. N. Gillis, D. Whittaker, L. H. Cronau and G. L. Hammond, manuscript submitted for publication.

occur non-enzymatically, but is catalyzed in liver and red blood cells [99] by the enzyme, glutathione-*S*-transferase, which also occurs in lung [101]. Therefore, the water-soluble product formed in our experiments [82, 98] may be the adduct of PGA_1 with GSH. The fact that PGE_1 (or $PGF_{2\alpha}$) does not react with GSH [99] explains our failure to detect water-soluble products in rabbit lung effluent when [^{3}H]PGE_1 is perfused [82]. It is, therefore, important to consider possible GSH adduct formation whenever PGA compounds are studied. The biological significance (or activity) of the PGA adduct is unknown, yet the widespread occurrence of glutathione-*S*-transferase in many tissues including lung [101] suggests that adduct formation with GSH or other sulfhydryl-containing molecules may play a role in metabolism of prostaglandins of the A series.

Bioassay techniques were used to demonstrate the release of newly synthesized prostaglandins from guinea pig lung in response to embolization [102], ventilation [103] or anaphylaxis [104]. An important question raised by these studies is how prostaglandins synthesized *de novo* in this manner escape metabolic degradation by PGDH unless they are produced in sufficient quantity to saturate the enzyme, which is unlikely [81]. One hypothesis to explain, partially, injury-induced release of prostaglandins is that the stimulus not only promotes prostaglandin synthetase activity [83, 104], but also somehow inhibits PGDH. For example, endotoxin-induced injury stimulates production of prostaglandins [105, 106] and also results in decreased PGDH activity in rabbit lung [107].

An appealing explanation for this inconsistency is the following. Samuelsson *et al.* [108] recently reported that the "prostaglandin-like" biological activity detected in effluent of lungs perfused with arachidonic acid (the precursor of bis-enoic prostaglandins) reflects the presence not only of prostaglandins and endoperoxide, but also a newly recognized and highly unstable compound, thromboxane A_2. The major portion of this activity, in fact, consisted of this very unstable substance. It is possible, therefore, that in the earlier studies referred to above [102–104] the biological activity ascribed to prostaglandins actually reflected the presence of thromboxane A_2.

In contrast to the experiments of Samuelsson *et al.* [108], which were carried out with guinea pig lung, Anderson *et al.* [109] found that [^{14}C]arachidonic acid, during a single passage through rat lung, is converted exclusively to material with the same chromatographic mobility as $PGF_{2\alpha}$. The total absence of $PGF_{2\alpha}$ metabolites in the latter experiments [109] is difficult to explain in light of the above discussion.

The cellular site of prostaglandin metabolism in lung has not been definitely established, although it is presumably intracellular since the volume of distribution and mean transit times of [^{3}H]$PGF_{1\alpha}$ in rat lung [110] and PGA_1 in rabbit lung [82] is greater than that of intravascular markers perfused simultaneously. A site close to the vascular space is consistent with the rapid appearance of PGE_1 or $PGF_{2\alpha}$ metabolites in venous effluent from lungs of various species [89, 90, 98] including man.* $PGF_{2\alpha}$ perfused in retrograde fashion through the pulmonary vein caused only one-fifth the vasoconstriction produced by the same concentration introduced via the pulmonary artery in cat lung [111]. The authors ascribe the differing sensitivity to metabolic degradation of $PGF_{2\alpha}$. Since the site of $PGF_{2\alpha}$-induced vasoconstriction is probably the small arterioles, their data also imply that the major site of metabolism could be the very large capillary bed of lung. Although the vascular endothelium within lung was recently proposed as a possible site for such metabolism [90], pulmonary arterial endothelial cells in culture apparently do not metabolize [^{3}H]$PGF_{1\alpha}$ (J. W. Ryan, personal communication).

If prostaglandin metabolism is inhibited, potentiation of the biological response to these substances might be anticipated. For example, aspirin, which at high concentrations inhibits PGE_1 metabolism by purified lung PGDH [112], also significantly enhances cardiovascular responses to $PGF_{2\alpha}$ in dog [113]. Several inhibitors of lung PGDH have been investigated, including prostaglandins of the B series, polyphloretin phosphate, diphloretin phosphate [85], stereoisomers of PGE_1 and C-7 oxa-$PGF_{1\alpha}$ [83, 114] as well as the anti-inflammatory drugs, indomethecin, phenylbutazone and meclofenamate [85]. However, phenylbutazone and aspirin did not affect PGE_2 metabolism by a purified preparation of rabbit lung [85]. In the case of diphloretin phosphate, it is possible that inhibition of metabolism actually reflects reduced transport of prostaglandin to intracellular PGDH, as recently suggested for $PGF_{2\alpha}$ [115].

Prostaglandin dehydrogenase of kidney has a short half-life [116]. If this is also true for the lung enzyme, then potential clearly exists for control of PG turnover at this level. Certainly, there is evidence that the capacity of lung to metabolize prostaglandins is modified by various conditions. For example, the activity of PGDH in lung (but not kidney or spleen) increases during pregnancy in rabbits [117]. On the other hand, endotoxin shock [107] or exposure to 100% oxygen [118], both of which, interestingly, cause early damage to endothelial cells, significantly reduces the metabolism of prostaglandins in lung.

CONCLUSIONS AND OUTLOOK

From the foregoing, it is apparent that lung is capable of removal and extensive degradation of circulating vasoactive hormones. There is little retention of unchanged hormones or their metabolites by lung and many of the processes outlined above seem well-designed to regulate the concentrations of prostaglandins, amines and peptides in blood before it reaches the systemic circulation. In addition to their actions at nonpulmonary sites, these hormones can change intrapulmonary blood flow and airway tone through their effects on vascular and airway smooth muscle; therefore, mechanisms for terminating such effects in lung assume considerable importance. Much evidence now points to the endothelial lining of lung blood vessels as possible sites for such regulation. Accordingly, changes in the available luminal surface area of endothelial cells or their function, caused by

*C. N. Gillis, D. Whittaker, L. H. Cronau and G. L. Hammond, manuscript submitted for publication.

drugs [7, 12] or disease [8, 9, 11], may considerably modify the metabolic capacity of these cells and, therefore, the delivery of vasoactive hormones both to the lung parenchyma and the systemic arterial vascular bed.

It remains for future research to establish definitively the role of lung as a metabolic organ. Before that point is reached, however, we will certainly require a clearer understanding of vasoactive hormone disposition by the lung, including its cellular basis and significance within the organ, as well as its contribution to the metabolic performance of the entire organism. With such information, the rationale for pharmacological intervention in these lung functions will become clear.

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