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Inflammatory Mediators and Asthma*

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I. Introduction

ASTHMA is characterized by variable and reversible airflow obstruction and by bronchial hyper-responsiveness, an excessive airway narrowing in response to a variety of apparently unrelated stimuli. Although contraction of airway smooth muscle has been emphasized as an important mechanism of asthmatic airway obstruction, it is now appreciated that edema of the airway wall resulting from microvascular leakage and luminal obstruction with plasma exudation and airway secretions may also be contributory. Inflammation in the airway wall has long been recognized as a prominent feature of fatal asthma attacks (234, 186), and recently similar changes have been found in bronchial biopsies of even mild asthmatics (331). There is now abundant experimental evidence that inflammation of the airways may lead to bronchial hyper-responsiveness (129), which is such a characteristic feature of asthma (89). These pathological changes are likely to be produced by the release of various mediators from inflammatory cells in the airways, and the purpose of this review is to discuss some of the inflammatory mediators which have been implicated. There is a vast and rapidly increasing literature dealing with these mediators, and knowledge is advancing very rapidly, made possible by greatly improved assays for mediators, by synthetic chemistry which provides pure forms of the mediators, and, perhaps most importantly, by the development of potent and specific antagonists, so that the contribution of each mediator to asthma can be evaluated. Because the literature is so extensive, we have chosen to concentrate on studies in human airways, although we have used data from animal studies when information about humans is not possible to obtain or is not yet available. It is now increasingly apparent that inflammatory cells, the generation of mediators, and airway responses are markedly different between species, and it is difficult to extrapolate from animal experiments to human airway disease. Although various animal models share some of the features of asthma, there is no entirely satisfactory model. It is, therefore, important that more research should concentrate on human asthma, despite the difficulties involved in such studies.

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A. Cellular Origin of Mediators

Many different inflammatory cells may release mediators, which interact in a complex way to produce inflammatory changes in airways (fig. 1).

1. Mast cells. For many years, mast cells have been assumed to play a central role in the pathogenesis of asthma; mast cell mediators, such as histamine, prostaglandin (PG) D_2, and sulfidopeptide leukotrienes, may explain several of the features of asthma (599, 496) (see table 1 for abbreviations). It is likely that immunoglobulin E (IgE)-dependent release of mediators from mast cells may account for the immediate bronchial response to allergen, and mast cells may also be involved in the bronchoconstrictor response to exercise, cold air, and fog. Recent evidence, however, questions their central involvement in bronchial hyper-responsiveness and chronic inflammation, since drugs which "stabilize" mast cells, such as beta-2 adrenoceptor agonists, do not prevent the late-phase response to allergen, nor the subsequent bronchial hyper-responsiveness. On the other hand, corticosteriods which do not have effects on mast

TABLE 1
Explanation of terms

Abbreviation	Definition
A23187	Calcium ionophore
AA	Arachidonic acid
AA-361	2,3,5-Trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone
ACE	Angiotensin converting enzyme
AGEPC	Acetyl glyceryl ether phosphorylcholine
AI	Anaphylatoxin inactivator
APRL	Anti-hypertensive polar renomedullary lipid
BN 52021	Ginkgolide B
BN 52063	Mixture of ginkgolides A, B, and C
CGRP	Calcitonin gene-related peptide
ECF-A	Eosinophilic chemotactic factor of anaphylaxis
ECP	Eosinophil cationic protein
EpDRF	Epithelium-derived relaxant factor
EPO	Eosinophil peroxidase
FMLP	Formyl-methionyl-leucyl-phenylalanine
FPL 55712	7-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylic acid monosodium salt
Gi	Inhibitory guanine nucleotide protein
H_2*	Second histamine receptor subtype
15-HETE	15-Hydroxy-5,8,11,13-eicosatetraenoic acid
HMWK	High-molecular-weight kininogen
HPETE	Hydroperoxyeicosatetraenoic acid
5-HT	5-Hydroxytryptamine (serotonin)
IgE*	Immunoglobulin E
IP3	Inositol 1,4,5-trisphosphate
L-649,923	(±)-4-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)propyl]thio-γ-hydroxy-β-methylbenzene butanoic acid
LT	Leukotriene
LTB_4*	Leukotriene B_4
LXA	Lipoxin A
MBP	Major basic protein
NAAGA	N-Acetyl-aspartyl-glutamic acid
NANC	Nonadrenergic, noncholinergic
NCA	Neutrophil chemotactic activity
NECA	N-Ethylcarboxamide adenosine
NKA*	Neurokinin A
NPK	Neuropeptide K
NSAID	Nonsteroidal antiinflammatory drug
OKY-046	Sodium (E)-3-[4-(1-imidazolymethyl)phenyl]-2-propanoate
PAF	Platelet-activating factor
PG	Prostaglandin
PGDH	15-Hydroxyprostaglandin dehydrogenase
PGI_2	Prostacyclin
PI	Phosphoinositides
PIA	Phenylisopropyl adenosine
PLA_2	Phospholipase A_2
REV 5901	α-Pentyl-3-(2-quindinylmethoxy)benzene methanol
SP	Substance P
SRS-A	Slow-reacting substance of anaphylaxis
Tc-DTPA	^{99m}Tc-diethylene triamine pentaacetate
TxA_2	Thromboxane A_2
U46619	9,11-Dideoxy-11α, 9α-epoxymethanoprostaglandin $F_{2\alpha}$
U-60,257	6,9-Deepoxy-6,9-(phenylimino)-delta-6,8-prostaglandin I_1
WEB 2086	3-[4-(2-Chlorophenyl)-9-methyl-6H-thieno)(3,2-f)(1,2,4)triazolo(4,3-α) diazepin-2-yl-1-(4-morpholinyl)-1-propanone]

* Variations of root abbreviation defined similarly.

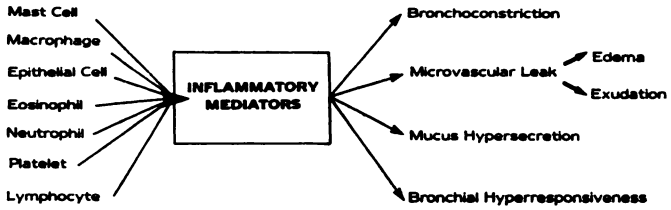

FIG. 1. Several different cells may be involved in the inflammatory process in asthma, leading to the production of many inflammatory mediators which, in combination, lead to the pathophysiological features of asthma.

cell mediator release are effective (139). This suggests that other inflammatory cells may be the source of mediators in asthma.

2. Macrophages. Macrophages are abundant throughout the respiratory tract, and recent evidence that they may be activated by IgE-dependent mechanisms has suggested their involvement in allergic inflammation (308). Macrophages from asthmatic patients release greater amounts of mediators, such as thromboxane, prostaglandins, and platelet-activating factor (PAF), than those derived from normal subjects. Interestingly, human lung macrophages are potently inhibited by corticosteriods (225).

3. Eosinophils. Eosinophil infiltration is a prominent feature of asthma (186) and differentiates asthma from other inflammatory conditions of the airway. Antigen inhalation results in a marked increase in eosinophils in bronchoalveolar lavage at the time of the late reaction (171), and there is a relationship between peripheral blood eosinophilia and bronchial hyper-responsiveness (216, 567). Eosinophils may release a variety of mediators, including leukotrienes (609) and PAF (344), and also release basic proteins, such as major basic protein and eosinophil cationic protein, which are toxic to airway epithelium.

4. Neutrophils. Neutrophils are also found in asthmatic airways and may release a number of mediators, including leukotriene B_4 (182), prostaglandins (245), PAF (378), and adenosine (386). In animal models of bronchial hyperresponsiveness, neutrophils have been implicated (418), but their role in asthmatic airways remains less defined than that of eosinophils.

5. Epithelial cells. Airway epithelial damage is a common feature of even mild asthma (331), and this may underlie bronchial hyper-responsiveness, since many of the conditions known to increase bronchial responsiveness (ozone exposure, upper respiratory tract viral infection, allergen exposure) are associated with epithelial damage. Loss of epithelial cells increases the bronchoconstrictor actions of spasmogens in vitro, possibly because airway epithelial cells release a relaxant factor (206, 55, 159) and will also expose sensory nerve endings, which may lead to local and cholinergic reflex bronchoconstriction (43). Epithelial cells may also themselves release inflammatory mediators, such as leukotriene B_4 (284) and 15-hydroxy-5, 8, 11, 13-eicosatetraenoic acid

(15-HETE) (291), which are chemotactic for inflammatory cells.

6. Platelets. Abnormalities in platelet function have been found in asthma, and animal studies suggest that platelets are involved in bronchial hyper-responsiveness (416). Platelets may release a variety of mediators such as serotonin, thromboxane, 5- and 12-lipoxygenease products, PAF, and oxygen-free radicals and may be activated by IgE-dependent mechanisms (307).

B. Mediator Effects

Inflammatory mediators may have a variety of effects on target cells in the airways, which may be relevant to asthma (fig. 2; table 2). They may lead to contraction of airway smooth muscle, either directly or indirectly, via release of secondary mediators or via neural mechanisms. They may also lead to increased secretion from submucosal glands, to increased fluid transport across airway epithelium, and to increased microvascular leakage, which results in edema of the airway and exudation of plasma into the airway lumen, which itself may result in the formation of new mediators (461). Inflammatory mediators may attract and activate inflammatory cells which themselves release a whole array of mediators which serve to perpetuate and emphasize the inflammatory response.

C. Mediator Receptors

Mediators produce their effects on target cells by the activation of specific cell surface receptors. More is now known about receptors for mediators in lung and the biochemical pathways involved in receptor activation (47). Using radioligand binding methods, it has been possible to characterize and localize these receptors in lung. It is hoped that further understanding of these receptors may lead to the development of more selective antagonists which will provide evidence for the role of a mediator in such a complex inflammatory disease as asthma. More is now understood about the biochemical pathways involved in pharmacological coupling in airway smooth muscle. Activation of some receptors leads to inhibition of adenylate cyclase via an inhibitory guanine nucleotide protein (Gi), whereas for other receptors, breakdown of membrane phosphoinositides (PI) leads to the generation of inositol trisphosphate (IP3) which releases intracellular calcium ions (76). Both mechanisms may be operative and may be interdependent. For muscarinic receptors, there is a close relationship between receptor occupancy and stimulation of PI turnover (249), and the same applies to receptors for inflammatory mediators (248).

D. Mediator Interactions

The role of each mediator itself is probably complex, but it seems likely that there is an even more complex interaction between different mediators, and that this may lead to hyper-responsiveness. Thus, inhalation of prostaglandins E_2, $F_{2\alpha}$, and D_2 may lead to increased responsiveness, to inhaled spasmogens (593, 224), although such an increase is only transient, whereas PAF leads to a more sustained increase in bronchial responsiveness (160), as discussed below.

Mediator interaction in the skin is well described (9), and mediators which lead to increased blood flow (such as PGE_2 and PGI_2) potentiate the plasma extravasation caused by other mediators (such as bradykinin) (63). Whether such interactions occur in the asthmatic airway is not yet certain.

Mediator interaction may also occur by "priming" of inflammatory cells. Thus, exposure of eosinophils to certain cytokines leads to augmented release of mediators (532). The number of possible interactions is almost limitless, and further research in this area should prove fruitful.

E. Mediator Antagonists

The most convincing way to elucidate the role of an individual mediator in a complex inflammatory process, such as asthma, is to study the effect of a selective mediator antagonist or an inhibitor of synthesis. Exten-

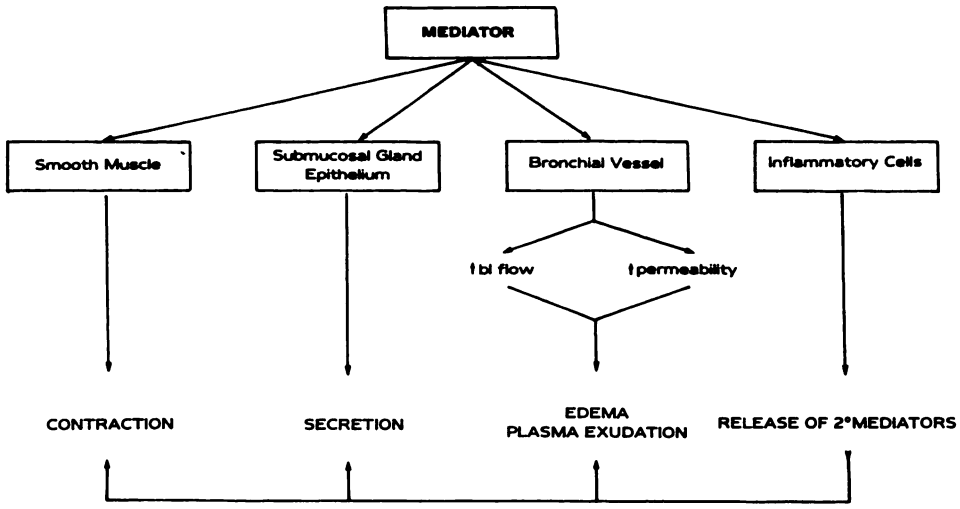

FIG. 2. Inflammatory mediators may have several effects on target cells of the airways, all mediated by activation of specific receptors.

TABLE 2
Effects of inflammatory mediators implicated in asthma

Mediator	Bronchoconstriction	Airway secretion	Microvascular leakage	Chemotaxis	Bronchial hyperresponsiveness
Histamine	+*	+	+	+	−
Prostaglandins D_2, $F_{2\alpha}$	++	+	?	?	+
Prostaglandin E_2	−	+	−	+	−
Thromboxane	++	?	−	±	+
Leukotriene B_4	−	−	±	++	±
Leukotrienes C_4, D_4, E_4	++	++	++	?	±
Platelet-activating factor	++	+	++	++	++
Bradykinin	+	+	++	−	−
Adenosine	+	?	?	?	−
Substance P	+	++	++	±	−
Neurokinin A	++	+	+	−	−
Complement fragments	+	+	+	++	−
Serotonin	±	?	+	−	−
Oxygen radicals	+	?	+	?	−

* Key: ++, pronounced effect; +, moderate effect; ±, uncertain effect; ?, information not available.

sive efforts by the pharmaceutical industry have led to the synthesis of several such agents which are currently being tested in asthma. Of course, any conclusions drawn from such studies must depend on the degree of selectivity of the antagonist. The dose of antagonist must also be adequate to block endogenously generated mediators and, at the very least, should be shown to block the effects of exogenously delivered mediator. Examples of the specific antagonists currently available are given for each mediator. The search for even more potent and specific antagonists may be beneficial to unravelling the components of asthma, but may not necessarily have a major clinical impact, since blocking a single mediator is unlikely to have a major effect if many different mediators are involved.

II. Histamine

Histamine was implicated in the pathogenesis of asthma shortly after its discovery, when it was shown to mimic anaphylactic bronchoconstriction in guinea pigs (167). Intravenous histamine caused bronchoconstriction in asthmatic subjects (473), and inhaled histamine was demonstrated to cause bronchoconstriction in asthmatic but not in normal subjects (154). Histamine is probably the best characterized of all mediators of asthma; there is now a wealth of information about its effects on human airways, and the recent introduction of specific and nonsedating antihistamines has made it possible to evaluate the role of histamine in asthma pathophysiology.

A. Synthesis and Metabolism

Histamine is formed by decarboxylation of histidine and stored in preformed cytoplasmic granules of mast cells and basophils in close association with proteoglycans which are predominantly heparin in mast cells and chrondroitin 4-sulfates in human basophils. Histamine forms 5 to 10% of the content of human mast cell granules. It is released from lung mast cells or blood basophils by an active secretory process which is calcium dependent, and several triggers to histamine release are recognized (215).

Histamine is metabolized by two major enzymatic pathways, and less than 3% is excreted unchanged in the urine. Fifty to 70% of histamine is metabolized to N-methyl-histamine by N-methyl transferase which is found in small intestine, liver, kidney, and leukocytes; and the remainder by diamine oxidase (histamine) to imidazole acetic acid in small intestine, liver, kidney, neutrophils, and eosinophils.

B. Histamine Receptors

Histamine produces its effects by interacting with specific receptors on target cells. The existence of more than one receptor subtype was suggested when Ash and Schild found that the classical antihistamine, pyrilamine (mepyramine), was able to block some responses, such as contraction of guinea pig trachea, but not others such as gastric acid secretion (29). The existence of a second histamine receptor subtype (H_2-receptor) was confirmed with the development of selective antagonists such as cimetidine and ranitidine. There is also a third subtype of receptor (H_3) for which selective agonists and antagonists have recently been developed (27).

1. H_1-receptors. H_1-receptors have been identified in animal and human lung homogenates by receptor binding techniques (114, 115, 250). Using an immunohistochemical technique to study the distribution of cyclic guanosine monophosphate, H_1-receptors have been localized to airway epithelial cells, macrophages, and alveolar cells in guinea pig lung, with surprisingly little localization to airway or vascular smooth muscle (520). In bovine tracheal smooth muscle, H_1-receptors have been determined by direct receptor binding using [^{3}H]pyrilamine and, using phenoxybenzamine to fractionally inactivate receptors, it has been possible to demonstrate that there are few "spare" histamine receptors (250).

The intracellular pathways involved in H_1-receptor activation have recently been studied. In guinea pig ileum, histamine stimulates breakdown of PI (180), and similarly in bovine tracheal smooth muscle, a corresponding response is found, with a close relationship

between H_1-receptor occupancy and PI response (248). The increase in cyclic guanosine monophosphate (GMP) which occurs in lung via H_1-receptor activation (471) is probably secondary to the increase in intracellular calcium, which occurs in response to PI hydrolysis and IP_3 formation.

2. H_2-receptors. H_2-receptors have been identified in lung using [^{3}H]tiotidine (213), but their localization has not been documented. H_2-receptor activation causes an increase in cyclic adenosine monophosphate (AMP) content of lung, and H_2-receptors are coupled to adenylate cyclase.

3. H_3-receptors. H_3-receptors have been differentiated using the selective agonist α-methyl histamine and the antagonist thioperamide, but the role of H_3-receptors in airway is not known; it is possible that they may be involved in feedback inhibition of histamine release. An atyptical histamine receptor-mediating relaxation, which is not blocked by combined H_1 and H_2 blockade, has been described in rabbit trachea (207).

C. Airway Effects

Histamine has several actions on the airway which mimic the pathophysiology of asthma, and for many years histamine was considered to be the major inflammatory mediator involved in asthma.

1. Airway smooth muscle. Bronchoconstriction was one of the first properties of histamine which was recognized (167) and histamine was shown to contract human bronchi in vitro many years ago, (511). Histamine contracts both large and small human airways in vitro (201) and, in animals, this contractile effect may be modulated by the presence of intact airway epithelium (206, 159). In vivo infused histamine causes marked systemic vasodilation but no bronchoconstriction (473, 299), whereas infused histamine causes bronchoconstriction in asthmatic patients (313, 557). Similarly, inhaled histamine causes bronchoconstriction in asthmatic patients more readily than normal subjects, as a manifestation of bronchial hyperreactivity (89). In vitro airways from asthmatics do not appear to be more responsive to histamine (119, 243), although there is one report of an increased maximal response to histamine (510). In animals, tachyphylaxis to the bronchoconstrictor effect of histamine may be demonstrated in vitro and may be due to the generation of prostaglandins, since indomethacin prevents its development (443). Tolerance to histamine challenge may also be found in mild asthmatic subjects, with a reduced bronchoconstrictor response to a second histamine challenge, which is prevented by prior treatment with indomethacin (388). Histamine releases prostaglandins from human lung in vitro (471), which may account for this effect.

There is some debate as to whether H_2-receptors are present in human airways. In several animal species, H_2-receptors which mediate bronchodilation have been demonstrated (123). Human peripheral lung strips may show a relaxant response to histamine, via H_2-receptors (589), although this could be an effect on pulmonary vascular smooth muscle rather than on airways. An H_2-selective agonist, impromidine, has no effect on normal or asthmatic airways in vivo (609a), and H_2-selective blockers, such as cimetidine and ranitidine, have not been associated with bronchoconstriction or increased sensitivity to bronchoconstrictors in normal or asthmatic subjects (571, 432, 96), although there is one report that cimetidine potentiates histamine-induced bronchoconstriction (425). A defect in H_2-receptor function has been demonstrated in allergic sheep (10), and there is evidence that H_2-receptor-mediated gastric secretion may be impaired in asthmatic patients (246), which supports the view that there may be a defect in H_2-receptors in hyperreactive airways (122).

2. Vascular effects. Histamine has a dual effect on human pulmonary vessels in vitro, with constriction mediated by H_1-receptors and vasodilation via H_2-receptors (86). Histamine increases bronchial blood flow in sheep and dogs, an effect which is mediated via H_2-receptors (369, 333).

Histamine also causes microvascular leakage in the bronchial microvasculature (507, 462), which is presumed to be due to contraction of endothelial cells in postcapillary venules (462). This effect is mediated via H_1-receptors and appears to be greater in larger rather than smaller airways (195). Although it has not been possible to study the effect of histamine on human bronchial microvasculature, it is likely that similar effects to those seen in animals will occur. Intradermal injection of histamine in humans causes immediate weal formation, which is completely inhibited by an H_1-antagonist (20, 557).

3. Airway secretions. Histamine increases secretion of mucus glycoproteins from human airways in vitro, and this effect is mediated by H_2-receptors since the effect is blocked by cimetidine and stimulated by dimaprit (524). The effect of histamine is rather weak when compared with other secretagogs. In canine airways, histamine also increases ion transport and water secretion via H_1-receptors (392).

4. Neural effects. In many species, the bronchoconstrictor effect of histamine is partially mediated by a vagal reflex, and histamine has been shown to increase action potentials in intrapulmonary vagal afferent nerves, an effect which is mediated by H_1-receptors (506). The role of cholinergic reflexes in the bronchial response to histamine in humans is less certain, since some groups have reported a significant reduction in the bronchoconstrictor response to inhaled histamine following anticholinergic treatment (524, 187), whereas others have not (118). It is likely that the vagal component of bronchoconstriction may be greater in normal subjects but becomes relatively less important in hyper-responsive airways.

5. Effects on other cells. Histamine increases the clear-

ance of small-molecular-weight compounds such as ^{99}Tc-diethylene triamine pentaacetate (Tc-DTPA) from human lungs, suggesting that it increases lung epithelial permeability, an effect mediated via H_2-receptors (96). The site of the increased clearance is not certain, but is more likely to be at the alveolar level than airway epithelium.

Histamine is also chemotactic to inflammatory cells, such as eosinophils (137, 577) and neutrophils (515), and may, therefore, amplify the inflammatory reaction, although the effects are small when compared to other mediators. Histamine stimulates T-lymphocyte suppressor cell function via H_2-receptors, and this function may be depressed in atopic individuals (69).

IgE-mediated release of histamine from human basophils is inhibited by histamine itself, acting on H_2-receptors, so that H_2-antagonists could theoretically enhance histamine release (365), but H_2-receptors have not been demonstrated on mast cells in human airways (312).

D. Role in Asthma

There is a wealth of evidence which implicates histamine in asthma, and the recent introduction of nonsedative antihistamines has made it possible to determine more precisely its contribution to asthma pathophysiology.

1. Histamine release. Measurements of histamine have been made in asthma since the first assays were developed in the 1940s. Fluorimetric assays, which lacked specificity and sensitivity, gave conflicting results, but refinement of radioenzymatic assays has made it possible to detect low concentrations of histamine in plasma (101). Several studies reported an elevated base-line concentration of plasma histamine in severe asthma (102, 126, 533), but the concentrations reported were very high, and it seems unlikely that they reported release from mast cells in lung, since such elevations should have caused marked cardiovascular effects (299). With improved sensitivity of the assay, it was shown that even mild asthmatic subjects had elevated values of plasma histamine (59, 49), which has been interpreted as mast cell "leakiness." Several conflicting results of plasma histamine measurements have been reported with various bronchoconstrictor challenges in asthma. Elevated plasma histamine has been reported in exercise-induced bronchoconstriction, but not in matched bronchoconstriction produced by hyperventilation (49), and it seems likely that the increase with exercise might be due to the increase in basophil counts which occurs during exercise (412). Plasma histamine accounts for only 0.5% of total blood histamine, the remainder being contained in basophils, so any contamination of plasma is likely to give marked discrepancies (298). Plasma histamine is also reported to be increased in allergen challenge in asthmatic subjects (285), and there may be a secondary rise associated with the late response (421) and also increases at night with the peak concentration corresponding to the time of maximum bronchoconstriction (57). Whether these increases in plasma histamine are a reflection of mediator release from airway mast cells is uncertain, however, and sampling blood from a peripheral vein is probably unlikely to closely reflect the relatively small amount of histamine release in airways, particularly in hyperresponsive patients where a comparatively small amount of histamine released locally may have a profound bronchomotor effect.

Recent studies have therefore measured histamine more locally in bronchoalveolar lavage fluid from asthmatics and demonstrated an elevated concentration in comparison with nonasthmatic subjects (208, 116), although in another study, no such elevation was found in mild stable asthmatics (481). While the above studies indicate that histamine may be released in asthma and thus provide indirect evidence of mast cell degranulation, they do not give information about the contribution of histamine to pathophysiology; this information can only be provided by the use of specific antagonists.

2. Antihistamines. If histamine is important in asthma, then antihistamines should be effective in its clinical management. Previous experience with antihistamines has not been encouraging in asthma (314), although the H_1-antagonists used have often lacked specificity, and sedative effects have limited the dosage.

Chlorpheniramine, given i.v. in a high dose, causes bronchodilatation in asthmatic but not in normal subjects (474, 188), although the sedative side effects would preclude clinical use. While inhaled chlorpheniramine was too irritant, a more potent H_1-antagonist, clemastine, given by inhalation caused bronchodilatation in some asthmatic patients (433, 571), confirming the existence of histamine "tone" in asthmatic airways and suggesting that there is some basal release of histamine in asthma.

H_1-antagonists have also been shown to partially protect against exercise-induced asthma (268) and antigen-induced bronchoconstriction (474).

The recent introduction of potent and selective nonsedative antihistamines, such as terfenadine and astemizole, has made it possible to more easily evaluate the role of histamine in asthma, since it is possible to achieve a greater degree of H_1-receptor blockade. Terfenadine causes a degree of bronchodilatation similar to that achieved with a beta-agonist, confirming the existence of histamine "tone" (144), and partially protects against exercise-induced asthma (452). Additionally, terfenadine has a small inhibitory effect against allergen challenge (121, 477), in doses which give a 30-fold shift in the bronchoconstrictor dose-response curves to histamine (478), suggesting that histamine plays a relatively minor role in immediate bronchoconstriction responses to allergen. Astemizole has a very long half-life and inhibits histamine, antigen, and exercise-induced asthma even 1

wk after discontinuing the drug (138, 282). Studies to assess the long-term effects of nonsedative H_1-antagonists in asthma are currently underway.

III. Cyclooxygenase Products

Since the identification and isolation of the first prostaglandins in the 1960s, the cyclooxygenase products of arachidonic acid (AA) (which include prostaglandins and thromboxane) have been implicated in asthma. Many aspects of the biochemistry and pharmacology of these compounds have been studied on lung tissue, which can generate, release, and inactivate them. Much information about the effects of cyclooxygenase products on the airways has been obtained in man.

A. Synthesis and Metabolism

Prostaglandins (PGs) are formed from arachidonic acid (AA), and initiation of PG biosynthesis occurs with its formation from cell membrane phospholipids by phospholipase A_2, which appears to be the rate-limiting step that determines the amount of substrate available for PG synthesis (336). Arachidonic acid is oxidized by cyclooxygenase to the cyclic endoperoxide, PGG_2, which is rapidly reduced to another unstable endoperoxide, PGH_2, which then gives rise to $PGF_{2\alpha}$, PGE_2, and PGD_2 (fig. 3). Other enzymatic pathways for cyclic endoperoxides lead to the formation of thromboxane A_2 (TxA_2) and prostacylin (PGI_2), which are both unstable and are rapidly hydrolyzed to the inactive but stable TxB_2 and 6-keto-$PGF_{1\alpha}$, respectively.

The main enzyme responsible for pulmonary metabolism of PGs is the 15-OH-PG dehydrogenase (PGDH) and, within one transit through the lung, inactivation of exogenous PGE_2 and $PGF_{2\alpha}$ is almost complete (402, 469), but PGI_2 is not removed to any significant extent

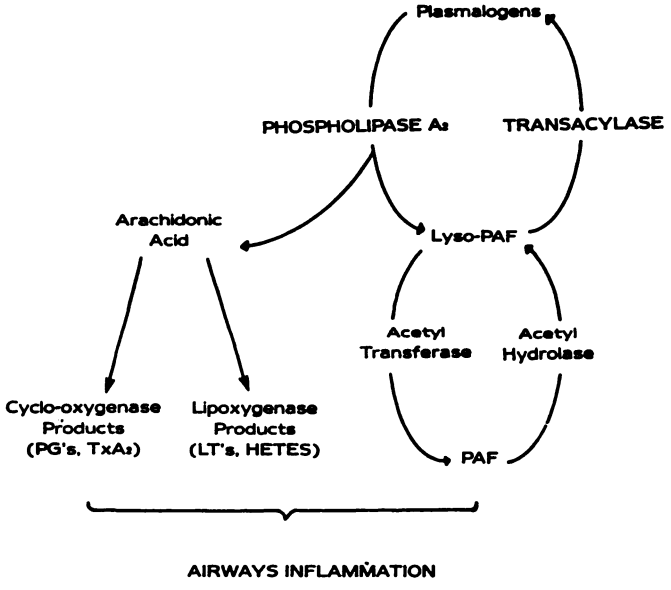

FIG. 3. Synthetic pathways leading to the synthesis of prostaglandins, leukotrienes, and platelet-activating factor from membrane phospholipids.

(296). This inactivation is a function of a selective and active uptake of PGs by capillary endothelial plasma membranes (80) and may be blocked by PG inhibitors such as indomethacin (80, 81). PGD_2 is a poor substrate for PGDH and, when infused i.v. in man, is metabolized to PGF-9 derivatives (67, 367), which may themselves have bronchoconstrictor actions (67).

PGD_2 and PGI_2 are released from human lung parenchyma during anaphylaxis, with smaller amounts of TxA_2, PGE_2, and $PGF_{2\alpha}$; by contrast, in the airway, PGI_2, $PGF_{2\alpha}$, and PGE_2 are released in the greatest amount (7, 513, 514). Steel et al. (549) suggest that prostaglandin generation accompanying anaphylaxis may result from a combination of factors, including direct release from mast cells, stimulation of H_1 histamine receptors in lung parenchymal cells, and as a nonspecific response to smooth muscle contraction.

Enriched or purified human lung mast cells undergoing IgE-dependent activation release PGD_2 as the major cyclooxygenase product (281, 364, 512). Human alveolar macrophages also release PGD_2 (380) in addition to measurable quantities of PGE_2, $PGF_{2\alpha}$, and TxB_2 (235). In vivo, local instillation of antigen in the airways of allergic asthmatics results in the immediate release of PGD_2 in bronchoalveolar lavage fluid (420). PGE_2 is released from canine airway epithelial cells when stimulated with bradykinin (353), and human pulmonary vascular endothelial cells are an important source of PGI_2 (301). Furthermore, circulating cells, such as platelets and neutrophils, may also contribute to the production of cyclooxygenase products, such as TxA_2 and PGE_2 (245, 427).

B. Receptors

Classification of the prostanoid receptors has been based primarily on comparisons of the rank orders of agonist potency (232, 322). Receptor classes have been identified according to their prostanoid effect, such as contractile/stimulant, relaxant/inhibitory, and irritant/coughing actions (232). On the other hand, Coleman et al. (140) have proposed that receptors exist for each of the natural prostanoids (i.e., the PGs D_2, E_2, $F_{2\alpha}$, and I_2 and TxA_2). At each receptor type, one of these natural prostanoids is most active, with the others being substantially weaker. With the use of selective antagonists and agonists of prostanoid contractile effects, Gardiner (231) has proposed 3 subtypes of the contractile/stimulant receptor with the following agonists (TxA_2, $PGF_{2\alpha}$, or PGD_2 and PGE_2), and Coleman et la. (140) suggest that there may be receptor subtypes for the PGE_2 and TxA_2 receptors. In human lung strips, all prostanoid contractile agonists appear to exert their effects via the thromboxane receptor; however, contraction of human bronchioles may be mediated via a novel prostanoid receptor which remains to be identified (403). PGI_2 receptors have been identified in lung homogenates by direct receptor binding (379), but the localization of these

receptors and the characteristics and distribution of other prostanoid receptors have not been determined.

C. Airway Effects

1. Airway smooth muscle. The prostanoids PGD_2, $PGF_{2\alpha}$, and TxA_2 contract human airway smooth muscle in vitro (83, 232, 560); PGE_1 (2, 523) and PGI_2 relax human smooth muscle (292), but this effect is small when compared to that of isoproterenol. PGE_2 can either increase or decrease basal tone of isolated human airway muscle preparations (230). In contrast to the guinea pig, endogenous prostanoids neither modulate the basal tone of isolated human airway smooth muscle (98, 169, 270), nor the contractile responses to acetylcholine or histamine (98, 270). This is also true of airways obtained from asthmatic patients (119). Adcock and Garland (5) reported a potentiation of histamine-induced contractions of small human bronchial muscle preparations by indomethacin, but this must be interpreted with caution because no appropriate controls were performed.

Inhaled $PGF_{2\alpha}$ causes a dose-dependent bronchoconstriction associated with coughing (430, 451, 538). Asthmatics are more responsive to the bronchoconstrictor effect of $PGF_{2\alpha}$ than normal subjects (398, 430). Thomson et al. (572) found a good correlation between the airway responsiveness to $PGF_{2\alpha}$ and that to methacholine, with $PGF_{2\alpha}$ begin 100-fold more potent than methacholine; aspirin-sensitive asthmatics were less sensitive to $PGF_{2\alpha}$. Tachyphylaxis to the bronchoconstrictor effects of $PGF_{2\alpha}$ has been reported in asthmatics (204, 398) but not in normal subjects. Sequential administration of high doses of $PGF_{2\alpha}$ may paradoxically result in bronchodilation, predominantly in the large airways (204).

On a molar basis, PGD_2 is approximately 3-fold more potent than $PGF_{2\alpha}$ and 30 times more than histamine as a bronchoconstrictor agent, and the duration of bronchoconstriction is more prolonged (266). Its effect is inhibited by a thromboxane receptor antagonist, suggesting that PGD_2 may act via the thromboxane receptor (68). There are no data in humans on the airway effects of TxA_2 or of its stable metabolite TxB_2, although in dogs, TxB_2 is slightly less potent than $PGF_{2\alpha}$ in causing bronchonconstriction (598). TxA_2 has been implicated in bronchial hyper-responsiveness in dogs, since a thromboxane synthetase inhibitor prevents the increased bronchial reactivity due to PAF (131), allergen (130), and ozone (11) in this species.

Both PGE_1 and PGE_2 are bronchodilators in both normal and asthmatic subjects and can reverse the bronchoconstrictor effect of $PGF_{2\alpha}$ (161, 317, 537). Bronchoconstrictor responses to both PGE_1 and PGE_2 have also been reported (277, 398, 536), possibly by stimulation of airway afferent vagal C-fibers (491). Even biphasic response to PGE_2 has been reported (591). Intravenous and aerosolized PGI_2 has no effect on resting pulmonary function in normal or asthmatic subjects at doses that inhibit platelet aggregation (77, 562) and increase plasma cyclic AMP (265). However, PGI_2 can prevent the bronchoconstrictor effect of ultrasonic mist and exercise (77), and PGD_2 (264), in asthmatic subjects.

The bronchoconstrictor effect of histamine, when administered immediately after $PGF_{2\alpha}$, is transiently potentiated in normal subjects (272, 593); similarly, both histamine and methacholine responsiveness are enhanced by PGD_2 in asthmatic subjects (224). However, $PGF_{2\alpha}$ reduces the subsequent response to histamine after the base-line tone has returned to normal 20 min later (203). Potentiation of cholinergic neurotransmission by a TxA_2 mimetic (U46619) has been demonstrated in canine airways (135), but it is not known whether this facilitating effect is seen in human airways. A similar effect has been demonstrated with $PGF_{2\alpha}$ (350, 528). By contrast, PGE_2 depresses cholinergic neurotransmission (592) and, therefore, cholinergic reflex responses in canine airways.

2. Secretion. In human airway tissue explants, PGD_2 and $F_{2\alpha}$ significantly increase mucous glycoprotein release (394, 485), while PGE_2 inhibits its release in one study (394) but not in another (485). In normal subjects, inhalation of $PGF_{2\alpha}$ causes increased airway secretions, with the production of mucous glycoproteins (370). The increase in mucous glycoprotein output induced by PGE_1 and $F_{2\alpha}$ in feline airways was from submucosal glands rather than goblet cells (489).

The effect of cyclooxygenase products on ion transport has been reported in animal tissues. Using the Ussing short-circuit technique, $PGF_{2\alpha}$ increased net chloride secretion, but PGE_1 decreased both chloride and sodium secretion in canine trachea (13). Bradykinin stimulates chloride secretion in the same tissue via the release of PGE_2 from airway epithelial cells (353). In bovine trachea, indomethacin reversed net basal transepithelial flow of sodium and chloride ions (338).

3. Inflammatory effects. The effect of cyclooxygenase products on airway vascular permeability is poorly documented. In the skin, PGE_1 and E_2 are poor inducers of edema but are potent vasodilators. However, the cyclooxygenase products, PGE_1, E_2, $F_{2\alpha}$, D_2, and I_2, can markedly potentiate histamine-, PAF-, and bradykinin-induced skin edema in several species including man (21, 63, 209, 610, 611). PGD_2 induces a wheal and flare response when injected into human skin, and histological examination reveals a perivascular neutrophil infiltrate as early as 30 min (545); this local cutaneous infiltrate is potentiated by leukotriene B_4 (LTB_4) (545). Some in vitro chemokinetic activity of PDG_2 (241) and of TxA_2 (547) for neutrophils has been reported. By contrast, PGD_2 and PGI_2 are both inhibitors of platelet function (391, 539). PGD_2 enhances the release of histamine from human basophils (465).

D. Role in Asthma

Increased plasma concentrations of a circulating metabolite of $PGF_{2\alpha}$ and TxB_2 have been observed imme-

diately after antigen-induced bronchoconstriction in asthmatic subjects (252, 527). In addition, increased levels of PGD_2 in bronchoalveolar lavage fluid have been detected during the acute response (420). Raised plasma levels of $PGF_{2\alpha}$ and PGE_1 have also been reported in asthma (428, 442).

Cyclooxygenase inhibition with aspirin or nonsteroidal antiinflammatory agents, such as indomethacin, has no effect on resting pulmonary function of asthmatic and normal subjects (202, 440). However, there is a distinct subgroup comprising approximately 5% of asthmatics ("aspirin-sensitive asthmatics") who experience symptomatic worsening after ingesting aspirin or nonsteroidal antiinflammatory agents. The bronchoconstrictor mechanism is unclear, but appears to be related to cyclooxygenase inhibition (561), and there is also evidence for platelet activation with aspirin (15). A minority of non-aspirin-sensitive asthmatics are improved by cyclooxygenase inhibitors (326, 484, 563). Inhibition of thromboxane synthetase by OKY-046 (see table 1), an imidazole derivative (297), has been reported to improve bronchial hyper-responsiveness in asthmatics (220), but this study needs to repeated with thromboxane receptor blockers (267, 441), because of the possible shunting of PGH_2 metabolism towards the synthesis of other cyclooxygenase products.

Cyclooxygenase inhibition with indomethacin or aspirin does not influence the early acute response induced by inhaled antigen in asthmatic subjects (196, 202, 527), despite suppressing the early rise in plasma TxB_2 (527). However, the late-phase response to antigen is inhibited by indomethacin, aspirin, or benoxaprofen (196, 527), and there is evidence that suppression of TxA_2 and the production of PGI_2 may contribute to this effect (527). These results, however, are not confirmed by a recent study, where an inhibitory effect on indomethacin antigen-induced airway hyper-responsiveness in asthmatics has been observed (324). These various clinical observations made with NSAIDs (see table 1) in antigen-induced asthmatics bring into question the precise relationship between late-onset responses and bronchial hyper-responsiveness.

In vitro studies of passively sensitized human bronchial strips have demonstrated an enhanced contractile effect of antigen by indomethacin, due to an augmented release of histamine, and perhaps of other mediators such as leukotrienes (4). Although indomethacin does not influence exercise-induced bronchoconstriction (502), it prevents the tachyphylactic bronchoconstrictor response to successive bouts of exercise (434).

Overall, there is reasonable evidence to suggest that cyclooxygenase products play a modulatory role in several aspects of airway function. Whether this role is beneficial or detrimental to the asthmatic airway depends on the predominance of the cyclooxygenase product because different products may have opposing effects. The availability of more specific antagonists of the prostanoids may help dissect their precise individual contribution to asthma.

IV. Lipoxygenase Products

Lipoxygenation of arachidonic acid gives rise to products with potent inflammatory effects which may be relevant to the pathophysiology of asthma. In particular, the leukotrienes, although identified in the late 1970s, were recognized as being biologically important in the 1930s when they were isolated in lung perfusates and named slow-reacting substance of anaphylaxis (SRS-A). The role of lipoxygenase products in human asthma is still undergoing evaluation, and the current availability of several leukotriene antagonists for human use has sparked further interest in lipoxygenase products.

A. Synthesis and Metabolism

Arachidonic acid may be oxygenated at different sites by specific lipoxygenases, initiating the formation of leukotrienes (LTs), lipoxins, and several hydroxyacids (HETEs) (fig. 4). The initial compounds generated from arachidonic acid are hydroperoxyeicosatetraenoic acids (HPETEs), which may either be reduced by peroxidases to corresponding monohydroxy acids (mono-HETEs), or be metabolized via other pathways. The mono-HETEs are the most common derivatives of arachidonic acid to be detected in the lungs, with 15-HETE being the most predominant (163, 259). Both the formation of 5-HPETE from arachidonic acid and the subsequent conversion of 5-HPETE to LTA_4 (see table 1 for abbreviations) are catalyzed by 5-lipoxygenase, which is selectively activated by challenge with antigen or the calcium ionophore A23187 (501). LTA_4 is unstable and is hydrolyzed enzymatically to the dihydroxyacid, LTB_4, or converted nonenzymatically into isomers of LTB_4. Alternatively, LTA_4 may be conjugated with glutathione to the peptidolipid LTC_4, first identified as a component of slow-reacting substance (SRS) in mouse mastocytomas (419). LTC_4 may be converted to LTD_4, a cysteinyl glycinyl derivative, by the action of γ-glutamyl transpeptidase (444). LTD_4 is further metabolized to the cysteinyl derivative, LTE_4, by the action of a dipeptidase (450). Conversion of LTE_4 to LTF_4 with the reincorporation of glutamic acid by γ-glutamyl transpeptidase has also been reported (16), but there is no evidence that LTF_4 is released from the human lung.

The generation of leukotrienes has been described from a number of tissues or purified cells (182, 358, 468). Among the human cell types that are of potential relevance to asthma, the profile and quantity of leukotrienes generated in vitro are dependent upon the cell type and the stimulus applied. For example, circulating neutrophils produce approximately 5 to 10 times more LTB_4 than LTC_4 when activated with the calcium ionophore A23187, but the ratios and quantities are reversed with normal eosinophils (609, 522). Even more LTC_4 is generated from patients with hypereosinophilia (609, 274);

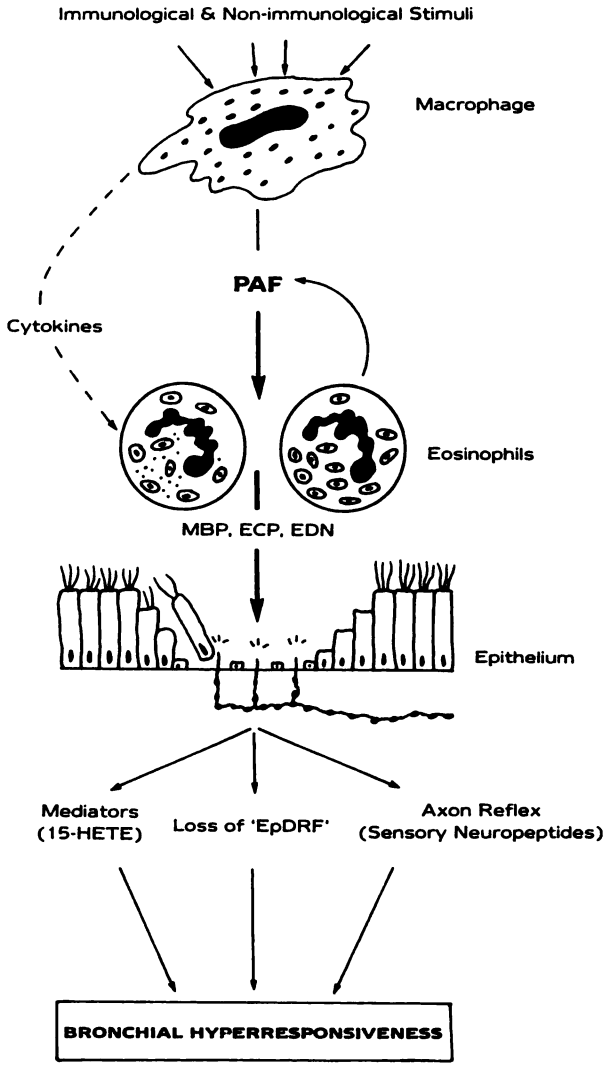

FIG. 4. Possible mechanism of bronchial hyper-responsiveness induced by platelet-activating factor (PAF). PAF may attract and activate eosinophils, which release basic proteins such as major basic protein (*MBP*), eosinophil cationic protein (*ECP*), and eosinophil-derived neurotoxin (*EDN*) which are toxic to airway epithelium.

in addition, eosinophils can also activate the 15-lipoxygenase pathway (274). On the other hand, alveolar macrophages generate 20 times more LTB_4 than LTC_4 (199, 396). Human lung fragments release mostly sulfidopeptide leukotrienes when activated by IgE-dependent mechanisms, but stimulation with the calcium ionophore also results in the formation of LTB_4 (354, 467). Highly purified human lung mast cells release less than 4 ng of LTB_4 per million mast cells after IgE-mediated activation compared to 10 ng of LTC_4 (358, 381); only small quantities of LTD_4 and LTE_4 are generated. Sulfidopeptide leukotrienes are released in vivo into nasal secretions of antigen-challenged allergic subjects (151). In vitro, allergen challenge of lung tissue from asthmatic subjects results in the release of LTC_4, D_4, and E_4 (163). Human monocytes can also generate substantial amounts of LTB_4 and LTC_4 on stimulation with the calcium ionophore A23187 (456). Tracheal epithelial cells from dog and human airways have been shown to generate LTB_4 and 15-lipoxygenase products (284, 291).

5-Hydroxyeicosatetraenoic acid (5-HETE) and other mono-HETEs are produced by stimulated neutrophils, together with LTB_4 (239). A whole series of di-HETEs and mono-HETEs are formed by eosinophils, but when stimulated by calcium ionophore A23187, 15-HETE becomes the predominant eicosanoid released by eosinophils (576). 12-HETE is the primary lipoxygenase product of platelets (330).

The transformation of LTC_4 to LTD_4 and LTE_4 represents a bioconversion rather than catabolism of leukotrienes and is an extremely efficient process (260). Catabolism of LTE_4 may occur at extrapulmonary sites, but LTE_4 can be partly excreted unchanged from the kidneys (445). Alterations in the peptide portion of LTC_4 do not usually result in a major loss of its biological activity (164). The sulfidopeptide leukotrienes released from neutrophils activated by phorbol myristate acetate are rapidly metabolized extracellularly by the concomitant formation of hypochlorous acid; this effect is prevented by the presence of a scavenger of hypochlorous acid, such as L-serine (341, 342). Eosinophils from hypereosinophilic patients can spontaneously inactivate LTC_4 also through the generation of hypochlorous acid (609). Inactivation of LTB_4 occurs mostly intracellularly in neutrophils by beta-oxidation with the involvement of a cytochrome P-450-like system (521), but the metabolites thus formed are still biologically active (282). Inactivation by ω-oxidation may occur in vivo (516). There is evidence to suggest that HPETEs and HETEs may inhibit the 5-lipoxygenase as well as cyclooxygenase enzymes (530, 584a).

Lipoxins are a newly described series of oxygenated derivatives of AA formed from interaction of the 5- and 15-lipoxygenase pathways, which were first isolated from neutrophils incubated with 15-HETE (517). Eosinophil-enriched leukcoytes also generate lipoxin A (LXA) when stimulated with calcium ionophore (518).

B. Receptors

The structural determinants of LTC_4 and LTD_4 for its contractile effects on guinea pig trachea and parenchymal strips have been studied (164, 106, 184, 361, 328). Studies of isomers of LTC_4 have demonstrated that differences in binding correspond closely with differences in contractile potency, supporting the concept that the lung binding site is a specific receptor (329). Functional studies suggest that these are discrete receptors for LTC_4 and LTD_4, since their molar ratios needed to elicit identical biological effects differ markedly in different tissues (360, 107), and since the contractile response of guinea pig lung parenchymal strips is biphasic to LTD_4 but not to LTC_4 (183). In addition, the compound FPL 55712 (see table 1) selectively antagonizes the effect of LTD_4 only (183). In the presence of serine borate, which inhib-

its the conversion of LTC_4 to LTD_4, FPL 55712 is unable to inhibit LTC_4-induced smooth muscle contraction (411).

Radioligand studies have also demonstrated two distinct binding sites in guinea pig lung homogenates, corresponding with the function of LTC_4 and LTD_4 receptors (280, 104). Autoradiographic studies have mapped the distribution of LTC_4 and LTD_4 binding sites in guinea pig lung, with LTC_4 receptors being more widely distributed and present in higher density than LTD_4 receptors (51). There is some evidence that a proportion of LTC_4 binding is to the enzyme glutathione-S-transferase (558). However, pharmacological studies suggest that normal human bronchi may not contain different receptors for LTC_4 and LTD_4 (106). It has been suggested that the majority of leukotriene receptors may reside in an intracellular pool and that they may be recruited to the plasma membrane during activation (358).

The selective suppression of the chemotactic responses of neutrophils to mono-HETEs by esters of mono-HETEs gives support for a receptor-mediated interaction between neutrophils and mono-HETEs (240). Cellular receptors to LTB_4 have also been postulated on the basis of functional and radioligand binding studies. Specificity of LTB_4 as a chemotactic agent for human neutrophils is supported by the fact that it is 30- to 300-fold more potent as compared with naturally occurring isomers (211, 362). In two studies, there was saturation of the binding of [^{3}H]LTB_4 to human neutrophils (244, 327), but the dissociation constant and number of specific binding sites reported differed significantly between these studies.

C. Airway Effects

1. Airway smooth muscle. The contractile effect of sulfidopeptide leukotrienes on human bronchial muscle has been carefully documented (165, 261, 303, 163, 510, 106). Leukotrienes C_4 and D_4 are approximately 1000-fold more potent than histamine in contracting human isolated bronchus (165), but are less active in human parenchymal strips (505). LTE_4 is less potent than LTC_4 and LTD_4, but its effects are more prolonged. LTB_4 also contracts human isolated bronchus, but rapid tachyphylaxis develops (505). 5- and 15-HETE cause modest contraction of human bronchial muscle in vitro (145). LXA causes long-lasting contraction of guinea pig lung strip, but is inactive on trachea (166).

In vivo, the effects of aerosols of LTC_4, D_4, and E_4 have been studied in normal and asthmatic subjects (283, 606, 607, 78, 41, 540, 323, 254, 168). As observed in animals, leukotrienes constrict both large and small airways (41, 540, 323). Inhaled LTC_4 and LTD_4 and 1000 to 5000 times more potent than histamine, with a longer duration of action (606, 607, 41). LTE_4 is approximately one-tenth as potent as LTD_4 (168), with a longer duration of action, is agreement with its in vitro effect. Asthmatic subjects are hyper-responsive to inhaled leukotrienes (540, 78, 6, 168). In one study (254), asthmatics did not display the same degree of hyper-responsiveness to LTD_4 as they did to histamine, but the measurement of responsiveness to leukotrienes may depend upon the lung function test chosen (6, 168). In contrast to their effect in the guinea pig, leukotrienes do not mediate their bronchoconstrictor effects through the release of cyclooxygenase products, in particular TxA_2 (163, 607, 303).

2. Secretion. Both LTC_4 and LTD_4 are potent stimulants of mucus release as measured by the output of mucus glycoprotein secretion from human airways in vitro, being 10-fold more potent than methacholine (393, 142). The mono-HETEs are less effective in causing mucus secretion in human airways (394).

In vivo, LTC_4 and LTD_4 enhance mucus secretion in the trachea of the dog (302); however, no effect was observed in the cat, except at extremely high doses (488). In the canine trachea, LTC_4, D_4, and E_4 (but not B_4) stimulate increased chloride secretion across the epithelium (354). Release of SRS-A during experimental canine anaphylaxis may be responsible for the slowing of mucus velocity caused by antigen inhalation (595). LTC_4 stimulates ciliary beat frequency of sheep airways in vitro, an effect mediated by cyclooxygenase products, possibly PGE_2 (594).

3. Vascular effects. Leukotrienes C_4, D_4, and E_4 increase microvascular permeability in the airways of guinea pigs (612, 286), being at least 100 to 1000 times more active than histamine (612), probably through a direct action at the postcapillary venular endothelial cell (162, 306). A leukotriene antagonist largely inhibits allergen-induced microvascular leakage in guinea pig airways (194). This effect of the leukotrienes is preceded by a phase of vasoconstriction (162), and the potentiation of the microvascular leakage by vasodilator prostaglandins, such as PGE_2 and PGI_2 (458), may be related to inhibition of vasoconstriction. However, in the human skin, LTC_4 and D_4 are potent vasodilators, producing wheal and flare responses at low concentrations (79, 109). LTB_4 also increases microvascular permeability (97), an effect that probably depends on the emigration and interaction of neutrophils through the endothelial microvasculature (97, 82, 604) and, in human skin, the increase in microvascular permeability induced by LTB_4 is increased by the vasodilator PGE_2 (21). LXA causes arteriolar dilation, but has no effect on microvascular permeability (166).

4. Effects of cells. LTB_4 is the most potent chemotactic and chemokinetic lipoxygenase product for neutrophils in vitro (161, 211), but is less effective for eosinophils (597). This action is not shared by the sufidopeptide leukotrienes. Intradermal injection of LTB_4 results in neutrophil accumulation into human skin, associated with a slow-onset tenderness and induration (545, 109). Leukotriene B_4 also stimulates the release of lysosomal enzymes (198) and enhances the release of oxygen radi-

cals from human neutrophils (519). It enhances the expression of surface complement (C3b) receptors on human neutrophils and eosinophils (421). Mono-HETEs also have been reported to stimulate the chemotaxis of human eosinophils and neutrophils, with maximal responses similar in magnitude to those evoked by C5a and formyl-methionyl peptides (242, 238), with 5-HETE being the most potent. 5- and 12-HETEs and LXA induce degranulation of human neutrophils (551, 517). 5-HPETE potentiates the release of histamine from human basophils (466).

5. Effect on bronchial responsiveness. Leukotrienes can increase the responsiveness of guinea pig tracheal muscle to histamine in vitro, although the effects seem to vary between the different sulfidopeptide leukotrienes (150, 345). This property may also be shared by 5-HETE (145). LTB_4 has been shown to augment bronchial responsiveness to acetylcholine in dogs (435). However, in man, prior inhalation of LTD_4 failed to increase the bronchoconstrictor effect of histamine (40), although LTE_4 may increase histamine airway responsiveness transiently in man (348). LTB_4 has no effect on bronchial responsiveness in man, even in the presence of PGD_2 (83a).

D. Role in Asthma

1. Leukotriene release. Sulfidopeptide leukotrienes can be detected in nasal secretions after allergen challenge in vivo (151) and in pooled plasma from subjects with acute asthma (616). Using a bioassay system, SRS-A has been measured in the sputum of allgeric asthmatic subjects (578), but there is doubt about the specificity of such an assay.

2. Inhibitors. Several studies have now examined the effect of pharmacological inhibition of lipoxygenase action or inhibition of leukotriene effects. Inhibition of LTC_4 and LTD_4 synthesis through an effect on glutathione S-transferase by U-60,257 (Piriprost) (37) blocks the nonhistaminic component of airway smooth muscle contraction induced by allergen in the bronchi of atopic asthmatic subjects in vitro, but had no effect on allergen challenge in asthmatic subjects in vivo (387). FPL 55712, the first recognized leukotriene antagonist (33), also attenuates allergen-induced bronchial contraction of human airways in vitro (3). In vivo, L-649,923 (see table 1) (304), an LTD_4 receptor antagonist, had only a marginal, nonsignificant effect on the early response to antigen and no effect on the late bronchoconstrictor response after antigen challenge (99). However, it is likely that, at the dose used, L-649,923 is only weakly effective against LTD_4-induced bronchoconstriction in vivo (42). FPL 55712, when inhaled by asthmatic subjects, had only a week bronchodilator effect in 2 of 4 subjects studied; however, this antagonist has only a short half-life and is also a phosphodiesterase inhibitor (349). Short-term treatment of asthmatic subjects with the 5-lipoxygenase inhibitor, 2,3,5-Trimethyl-6-(12-hydroxy-5,10-dodecadiynyl)-1,4-benzoquinone (AA-361) (615), had no effect on the airways hyper-responsiveness of asthma (220). Another 5-lipoxygenase inhibitor, REV 5901 (see table 1) (585), which is also a leukotriene receptor antagonist, caused no bronchodilatation when inhaled by asthmatic subjects (189), and there was no antagonism against LTD_4-induced bronchoconstriction. Colchicine, an antiinflammatory agent, has been shown to inhibit LTB_4 production from human neutrophils in vivo, yet has no effect on either early or late-phase response to allgergen (464).

The use of dietary supplementation with eicosapentaenoic acid (fish oil) to decrease the formation of lipoxygenase products by diversion to the less active eicosapentaenoic derivatives, such as LTB_5, C_5, and D_5 (346), has also been studied in asthma. Despite the fact that leukocyte function was attenuated in terms of LTB_4 biosynthesis and chemotaxis, no clinical benefit was observed (24).

The role of the lipoxygenase products, including leukotrienes, in asthma, therefore, still remains unclear, perhaps largely through the difficulty in obtaining convincing pharmacological inhibition of their effects. Although the leukotrienes are potent in causing smooth muscle contraction, airway microvascular leakage, and mucus secretion, they are not capable of inducing persistent bronchial hyper-responsiveness. Apart from LTB_4, the other leukotrienes do not possess significant chemotactic activity for eosinophils.

V. Platelet Activating Factor

In 1966 it was observed that there was a complement-independent release of histamine into plasma (in rabbits undergoing an acute allergic response) (39). As platelets had previously been demonstrated to be the major source of histamine in this species (290), this suggested the formation of a mediator capable of inducing platelet activation in the allergic response. This histamine release was the consequence of an IgE-dependent activation of basophils, which in turn released a soluble product capable of eliciting platelet activation (74). This basophil product was termed platelet activating factor (PAF) and has been chemically characterized as an ether-linked phospholipid, 1-O-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine. PAF has a number of synonyms, including Paf-acether (75), acetyl glyceryl ether phosphorylcholine (AGEPC) (172), or anti-hypertensive polar renomedullary lipid (APRL) (84). PAF has many biological properties in addition to platelet activation and is particularly interesting as a putative mediator of asthma, since it can induce several characteristic features of asthma (415, 52, 53, 95).

A. Origin

1. Synthesis. The synthesis of PAF is not secondary to cell damage or physical disruption (568), suggesting that PAF is neither preformed nor stored but rather synthesized denovo. Two distinct synthetic pathways have been described for PAF (542, 543). The first is a

two-step pathway which has been demonstrated in a number of inflammatory cell types in vitro, including macrophages (404, 431, 14), neutrophils (371, 309), eosinophils (344), and platelets (73, 125), and which involves the production of the biologically inactive intermediate, lyso-PAF, from ether-linked phospholipids by the action of phospholipase A_2 (PLA_2) (fig. 3). This step is in common with the liberation of arachidonic acid for the subsequent formation of cyclooxygenase and lipoxygenase metabolites (fig. 3). Formation of lyso-PAF is abolished by PLA_2 inhibitors, such as bromophenacytyl bromide (586), hydrocortisone, and macrocortin (449). In order to synthesise PAF, a second enzyme has to be concomitantly activated with the PLA_2, namely an acetyl coenzyme A (CoA)-dependent acetyltransferase enzyme, which has been described in a number of inflammatory cell types and is the rate-limiting step for PAF production by this pathway (542, 543).

A second synthetic pathway for PAF involves the enzyme, cholinephosphotransferase, which can synthesize PAF directly from ether-linked phospholipids (542, 543). The levels of this enzyme are generally much higher than the comparable acetyl transferase levels, and particularly so in lung. The cholinephosphotransferase pathway may be required to maintain physiological levels of PAF for normal cell function, particularly in the regulation of blood pressure, whereas the rate-limiting acetyl transferase pathway is only activated in response to inflammatory signals such as phagocytosis or chemotaxis (543). Most of these data originate from in vitro observations and, to what extent these two synthetic pathways contribute to PAF formation in vivo, remains to be elucidated. The availability of a number of acetyl transferase inhibitors, such as L-648-611, may help to elucidate the precise role of this synthetic pathway in both phyisology and pathophysiology (490).

2. *Cellular origin.* Although PAF was originally described as a product of rabbit basophils, it can also be produced by a number of other inflammatory cells. Interestingly, in man PAF does not appear to be an extracellular product of basophils or mast cells and, although pulmonary mast cells have the capacity to synthesize PAF, it appears to be retained intracellularly (366). This phenomenon has also been observed in human neutrophils, but the precise role of the intracellular PAF is uncertain (378). Three to 4% of the synthesized PAF is released within a few minutes of activation of neutrophils by triggers such as opsonized zymosan or calcium ionophore. Human platelets produce lesser amounts of PAF than neutrophils but approximately 50 times more lyso-PAF, presumably associated with the production of arachidonic acid metabolites following PLA_2 activation. Eosinophils isolated from patients with eosinophilia release PAF following stimulation with various chemotactic factors, including eosinophilic chemotatic factor of anaphylaxis (ECF-A) and f–Met–Leu–Phe, suggesting that PAF release may play a central role in the chemotaxis of human eosinophils (344, 531). Human alveolar macrophage obtained by bronchoalveolar lavage of allergic asthmatics also release PAF following stimulation with the appropriate antigen in vitro (26). Interestingly, zymosan does not release PAF from human alveolar macrophages, despite an increase in phagocytic activity in such cells. However, it remains possible that PAF is being synthesized in these cells but is being retained intracellularly in an analogous manner to that observed in phagocytosing neutrophils.

Cultured human vascular endothelial cells also release PAF following stimulation with thrombin, calcium ionophore, leukotrienes, histamine, bradykinin, ATP, or monocyte-derived interleukin 1 (475). As with other cell types, some of the PAF formed by endothelial cell monolayers remains cell associated rather than being released extracellularly in situations where PGI_2 production can be detected. Preliminary data show that PAF is synthesized by human epidermal cells obtained from psoriatic lesions (153), but whether airway epithelial cells synthesize PAF has not been determined.

3. *Metabolism.* PAF is very rapidly metabolized by the action of the enzyme phosphatidyl-2-acetyl-hydrolase, which removes acetate and leads to the formation of lyso-PAF (197). Thus, the primary metabolite of PAF is also its precursor in some situations, and in some cell types there is a constant cycle of PAF synthesis and metabolism (575). The acetylhydrolase enzyme responsible for the initial metabolism of PAF has been identified in the plasma of a number of mammalian species, including man, and is extremely active. From studies in the rabbit, 70% of the PAF is metabolized to lyso-PAF 1 min after i.v. injection (339). An acetylhydrolase enzyme (which is capable of metabolizing PAF) has also been reported to be present on the surface of platelets, which is released following activation with PAF (559). Acetylhydrolase activity in plasma from asthmatic children is significantly reduced compared with healthy controls, suggesting that PAF may have protracted biological activity in these subjects (409). Lyso-PAF can be further metabolized by the removal of the O-alkyl group by an enzyme similar to the well-characterized tetrahydropteridine-dependent alkyl monooxygenase enzyme isolated from hepatic tissue, which metabolizes lyso-PAF to a fatty aldehyde and glyceryl-3-phosphorylcholine (343).

B. Receptors

There are a number of indications that PAF exerts its biological effects via specific membrane receptors. PAF is both highly potent, acting on some tissues in concentrations as low as 10^{-8} M, and is stereoselective (94). PAF also exhibits specific tachyphylaxis, which again suggests an action via specific receptors (334). There have also been a number of studies using [^{3}H]PAF as a radioligand, which have demonstrated high affinity, saturable binding sites for PAF on human platelets (583), neutrophils (584), and lung membranes (295). Such specific binding

is inhibited by a number of PAF antagonists, but there is a high degree of nonspecific binding which makes these experiments difficult to interpret. Recently, labeled PAF antagonists, such as [^{3}H]kadsurenone and [^{3}H]WEB 2086 (see table 1), have proved more useful as radioligands (294, 580). Although none of the above evidence is definitive proof of the existence of a PAF receptor, a number of studies have reported that the binding of PAF appears to correlate with its biological effects (95). A protein has been isolated containing the PAF receptor from human platelets (582).

Experiments showing different affinities of the PAF antagonist, kadsurenone, in peritoneal macrophages and blood leukocytes, have suggested the existence of more than one receptor subtype (335), although in this study cells obtained from two different species were compared. Another study has reported that certain effects of PAF (e.g., induction of neutrophil adhesion) are not blocked by PAF antagonists at concentrations which clearly antagonize other biological activities of PAF (590). Whether PAF-receptor subtypes exist is still not certain, but is an important issue since antagonists may not block all the effects of PAF.

C. Airway Effects

1. Airway smooth muscle. PAF is as one of the most potent inducers of bronchoconstriction in both experimental animals and man (416, 160, 501a). However, PAF does not posess direct contractile effects on human airway smooth muscle preparations in vitro, yet may elicit contraction of airway smooth muscle preparations provided platelets are present in the organ bath (509, 120). In experimental animals, PAF-induced bronchoconstriction is secondary to platelet activation, since bronchoconstriction is abrogated in animals previously rendered thrombocytopenic by the use of a selective cytotoxic antibody (587, 258). The nature of the platelet-derived spasmogen is not known, and there is controversy about the effects of antihistamines, 5-hydroxytryptamine (5-HT) antagonists, and inhibitors of arachidonic acid metabolism (both cyclooxygenease and lipoxygenase) (587, 87, 357). Neutrophils have also been implicated in PAF-induced bronchoconstriction (325), and there is a very close anatomical relationship between platelets and neutrophils observed throughout the pulmonary vasculature of experimental animals following systemic treatment with PAF (174). As neutrophils and platelets have been observed to cooperate in the formation of novel biologically active materials (382, 390), it is conceivable that such products contribute to PAF-induced bronchoconstriction.

PAF induces contraction of rabbit (110) and guinea pig lung strip preparations in vitro, which may depend in part upon the release of acetylcholine from cholinergic nerves (556) or on the release of thromboxane (351). However, in addition to airway smooth muscle, these preparations also contain vascular smooth muscle and other contractile elements and are not necessarily the best preparations for studying airway smooth muscle function.

In humans, PAF administered by inhalation is a potent bronchoconstrictor, having a rapid onset of action and recovery over 2 h, whereas lyso-PAF has no significant effect (160). The bronchoconstriction induced by PAF in man is tachyphylactic, preventing cumulative dose-response studies. Surprisingly, there is no relationship between the airway responsiveness to PAF and that to a cholinergic agonist in normal subjects (160). This is in contrast to all other bronchconstrictor stimuli, such as histamine, LTs, and PGs, in which there is a good correlation with the sensitivity to methacoline (89). Even in asthmatic patients showing hyperresponsiveness to metacholine, the airway responsiveness to inhaled PAF is similar to that observed in normal subjects (134, 501a).

2. Airway secretions. There are few reported studies investigating the effect of PAF on airway secretion. PAF increases mucus secretion in the trachea of ferrets both in vitro and in vivo (337), and also weakly stimulates mucus glycoprotein from explants of human airways in vitro (247). PAF induces an increase in the protein content of airway secretions, although no alternation in mucus output (499, 463). It is likely that the increased protein content is secondary to plasma protein extravasation into the airways, as PAF is known to have marked effects on airway microvascular permeability (see below). Recent studies in isolated porcine trachea have demonstrated increased mucus secretion following PAF administration, which was unaffected by antagonists of histamine, acetylcholine, and LTD_4 or by inhibitors of PG and LT synthesis (550). Also, PAF has been observed to stimulate secretion of mucus in explants of rodent airways in organ culture (8). PAF, administered intratracheally or intravenously, slows mucociliary transport, which may result from an effect on ciliated respiratory epithelial cells, or from exudation of plasma into the airway lumen (35).

3. Vascular effects. PAF induces microvascular leakage in several tissues including skin (453, 454, 289, 19–23) and airways (191, 436) at doses over 1000 times lower than that of histamine. In man, the effect of PAF on microvascular permeability has been studied in the skin, where PAF elicits a classical acute wheal and flare response (64, 23, 408, 133). The wheal response is unaffected by prior treatment with H_1-antagonists (although the flare response is) or cyclooxygenase inhibitors, suggesting that this effect is not secondary to liberated histamine or cyclooxygenase metabolites (20). Increased vascular permeability is partly dependent on local blood flow, and the addition of local vasodilators, such as PGE_1 or PGE_2, potentiates PAF-induced vascular permeability in the skin (19). It is less certain whether such an action is important in the bronchial circulation which normally has a high basal blood flow.

PAF-induced vascular permeability appears to be independent of platelet or neutrophil activation (414, 454, 470), despite the fact that PAF induces sequestration of both platelets and neutrophils in the cutaneous microvasculature (174). Since endothelial cells have PAF receptors (108), it is quite likely that PAF has a direct contractile effect on endothelial cells. PAF-induced vascular permeability can be inhibited in both experimental animals and man by PAF antagonists, suggesting that PAF is acting via specific PAF receptors (133, 273, 192). PAF has potent effects on airway microvascular permeability; as little as 1 ng/kg administered i.v. to guinea pigs induces a rapid extravasation of Evans blue dye (as a marker of plasma-albumin) in central and peripheral airways (191, 436). As in the skin, this is a direct effect of PAF, since it is not reduced by platelet depletion, cyclooxygenase inhibition, or antagonists of histamine or leukotrienes (191), but is inhibited by PAF antagonists (191, 192). PAF induces delayed leakage of plasma proteins into the airways, which may be inhibited by anti-asthma drugs such as cromolyn sodium and theophylline (462).

4. Inflammatory cell activation. PAF activates a wide range of inflammatory cells, both in vitro and in vivo. In vitro, PAF induces aggregation of platelets (74), neutrophils (210, 439), and monocytes (614), with subsequent release of secondary inflammatory mediators, including lipoxygenase and cyclooxygenase products, oxygen radicals, and lysosomal enzymes. PAF also induces the chemotaxis of neutrophils (439, 597) and eosinophils (344, 531, 564, 597). The response of eosinophils to PAF is of particular interest in the context of asthma, as PAF represents the most potent chemotactic stimuli for human eosinophils so far described (344, 531, 564, 597). Other eosinophil chemotactic stimuli, such as ECF-A and formyl-methionyl-leucyl-phenylalanine (FMLP), may act via the release of PAF, suggesting that PAF may play a central role in the chemotactic response of eosinophils (344, 531). In addition, PAF induces the formation of LTC_4 from eosinophils (103), and PAF antagonists inhibit IgE-dependent activation and release of oxygen radicals from eosinophils, suggesting that PAF may be involved in allergic stimulation of this cell type (112). PAF causes much greater activation of eosinophils from asthmatic patients than from other atopic patients (124), and human eosinophils have a high density of PAF receptors (580). PAF also activates macrophages, with release of oxygen radicals (269).

In vivo, PAF results in the recruitment of various inflammatory cells into tissues following either systemic or local adminstration. After intradermal administration of PAF in normal volunteers, there is a substantial inflammatory cell infiltrate characterized at 4 h by neutrophils, and at 24 h by a mixed cellular infiltrate comprising both neutrophils and mononuclear cells (22), whereas in atopic subjects the cellular infiltration is characterized by activated eosinophils and is reminiscent of antigen-induced eosinophil infiltration in the same subjects (275). This suggests that allergic subjects respond differently to PAF in comparison with healthy individuals. Since the rate-limiting acetyltransferase enzyme involved in PAF production is switched on in eosinophils obtained from individuals with eosinophilia compared with healthy subjects (344), these observations indicate that PAF should be considered as a primary mediator involved in the induction and maintenance of the eosinophilic infilitration observed in allergic patients. Thus, PAF antagonists inhibit antigen-induced eosinophil infilitration in sensitized animals (149, 148, 356).

Preliminary studies indicate that inhalation of PAF by normal volunteers results in an increased recovery of neutrophils in bronchoalveolar lavage fluid at 6 hr accompanied by activation of neutrophils in the circulation (596). In animals, PAF, administered both locally and systemically, induces an eosinophilic-rich infiltrate in the lungs (25, 148, 149).

PAF also induces an extravascular recruitment of platelets into pulmonary tissue, where they are observed to be in close apposition to both airway smooth muscle and infiltrating eosinophils (355). Such pathological changes have also been reported in allergic animals and have been identified in bronchoalveolar lavage fluid obtained from allergic asthmatics (407). The contribution of extravascular platelets to the pathology of asthma has yet to be fully elucidated, but platelet depletion inhibits both PAF and antigen-induced eosinophil infilitration in the lungs of animals (356) and reduces PAF-induced bronchial hyperreactivity in the guinea pig (400). As platelets are a good source of smooth muscle mutogens, such as platelet-derived growth factor (500), they may contribute to the hyperplasia of bronchial smooth muscle observed both in animals chronically treated with PAF (405) and in asthmatic patients at autopsy (271).

5. Bronchial hyper-responsiveness. One of the most important properties of PAF is its ability to induce a nonselective and long-lasting increase in bronchial hyper-responsiveness in both experimental animals and man. PAF has been shown to elicit increased bronchial responsiveness in guinea pigs (400, 58, 494, 495, 205), dogs (131), sheep (128), and normal human subjects (160, 501a). In guinea pigs, the increased responsiveness is dependent upon the presence of circulating platelets, since platelet depletion with a specific cytotoxic antibody abrogates PAF-induced bronchial hyper-responsiveness (400), whereas selective depletion of neutrophils is without effect (413).

In man, the maximal increase in bronchial responsivness to methacholine occurs 3 days after a single exposure to PAF and may persist in some individuals for up to 4 wk. Because PAF is rapidly inactivated in the airways, such long-lasting changes must result from secondary mechanisms which are currently under investi-

gation. Although PAF elicits airway hyper-responsivness to a wide range of spasmogens, including histamine, acetylcholine, serotonin, and substance P, the increased responsiveness is not secondary to alterations in receptor number, affinities, or post-receptor transduction mechanisms (at least for acetylcholine and histamine in the guinea pig) (495). PAF has, however, been observed to elicit a down-regulation of beta-adrenoceptors in rat brain (92) and human lung in vitro (9), a phenomenon which may contribute to bronchial hyper-responsiveness and which is a feature of astmatic airways in vitro. However, in guinea pigs made hyper-responsive following treatment with i.v. PAF, there is a reduced bronchodilator response to isoproterenol in vivo, but the in vitro responsiveness of tracheal smooth muscle to isoproterenol and tracheal and lung beta-receptor density remain unchanged (58). This suggests the impaired bronchodilator response to a beta-agonist in vivo is not due to impaired beta-adrenoceptor function and is more likely to be due to airway edema, which would not be reversible by a beta-agonist.

PAF-induced bronchial hyper-responsiveness may be a consequence of eosinophil infiltration (fig. 4), and the degree of blood eosinophilia is closely related to the degree of bronchial hyper-responsiveness (216, 567). Eosinophils release cytotoxic materials, such as major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil peroxidase (EPO) which may lead to damage of airway epithelium (216). Epithelial disruption is a common feature of asthma, and loss of epithelium may contribute to airway hyper-responsiveness by loss of an epithelial-derived relaxant factor (206, 55, 159), by exposure of sensory nerve endings (43), or by the loss of enzymes which metabolize sensory neuropeptides (219). Loss of epithelium could also explain the impaired bronchodilator response to beta-agonists in vivo following administration of PAF in the guinea pig, since beta-agonists have a reduced effect on airway smooth muscle preparations denuded of airway epithelium (206, 55).

D. Role in Asthma

1. Release of PAF in asthma. The precise role of PAF in asthma remains unknown, although PAF may reproduce many features of asthma. The detection of PAF in biological fluids has been hampered by the lack of a simple assay system. Most attempts to measure PAF in biological fluids have relied upon the bioassay developed by Henson and Pinckard (276), which is based upon the fact that PAF is able to selectively desensitize platelets to itself in vitro. A number of investigators have used their technique to show that a PAF-like material is released into the circulation concomitantly with antigen-induced bronchoconstriction (570, 70). PAF has also been detected in bronchoalveolar lavage fluid of asthmatics using this bioassay technique (146) and in blood of allergic asthmatics undergoing allergen-induced late-onset responses (423).

2. PAF antagonists. A more feasible approach is the use of specific PAF antagonists, several of which are now available and some are undergoing clinical trials. PAF antagonists inhibit several of the effects of PAF which are relevant to asthma, including eosinophil activation (597), bronchoconstriction (173, 526), bronchial hyperresponsiveness (149, 279), and airway edema (191, 192). PAF-antagonists also inhibit certain aspects of allergic responses in both experimental animals and man. Ginkgolida B (BN 52021) and WEB 2086 inhibit allergen-induced bronchoconstriction in sensitized guinea pigs (93, 117), and BN 52021 reduces the eosinophil activation and bronchial hyper-responsiveness resulting from allergen challenge (149, 356). Furthermore, in ragweed-sensitized rabbits, BN 52021 inhibits late-onset airways obstruction and the increased bronchial hyper-responsiveness following allergen challenge (148). However, PAF antagonists do not inhibit propranolol- or indomethacin-induced bronchial hyperresponsiveness in guinea pigs (179).

Clinical studies with PAF antagonists are still in their infancy (132), but the ginkoglide mixture, BN 52063 (see table 1), appears to function as a selective PAF antagonist in man (133) and inhibits the late-phase cutaneous response to allergen in atopic subjects, which is associated with eosinophil infiltration and has some similarity with the pathology of the late-onset airways obstruction observed in allergic subjects (493). This suggests that PAF may be involved in the late-onset allergic response in man. BN 52063, when taken orally, has recently been shown to be only a modest antagonist of PAF-induced bronchoconstriction in human airways (492), and therefore more potent antagonists may be necessary to evaluate airway disease. Clinical trials of BN 52063 in asthma are currently under way (255, 132).

VI. Kinins

Bradykinin and related kinins are formed from plasma precursors as part of the inflammatory response, yet there is relatively little information about the involvement of these potent vasoactive peptides in asthma. Bradykinin itself was first isolated in 1949 from enzymatic treatment of blood (497), and later shown to be a nine amino acid peptide. Lysine-bradykinin (kallidin) has also been identified and has similar pharmacological properties (483).

A. Formation and metabolism

Bradykinin is generated from α-2-globulins, called kininogens, in plasma by the action of enzymes (kininogenases) which are produced by the liver (plasma kallikrein) and by other tissues (tissue kallikrein). In addition, human lung mast cells and basophils release a kininogenase, which is distinct from kallikreins (476), and which may be identical to tryptase. Both a high-molecular-weight kininogen (HMWK) and a low-molecular-weight kininogen are recognized, the former probably acting as a substitute for plasma kallikrein, and the

latter for tissue kallikrein, since it is formed extravascularly.

Bradykinin and lys-bradykinin are inactivated by various proteolytic enzymes, but the major pathways involve kininase I (carboxypeptidase N) and kininase II (angiotensin converting enzyme; ACE), the latter enzyme being localized to endothelial cells. ACE inhibitors, such as captopril and enalapril, by preventing the action of kininase II may enhance the effects of endogenous bradykinin. Thus, enalapril increases the vascular effects of bradykinin in human skin (228). However, another potent ACE-inhibitor (ramipril) has no effect on the bronchoconstrictor effect of bradykinin (178), suggesting that ACE is not an important mechanism for degradation of bradykinin in human airways. Nor is the effect of bradykinin on human bronchi enhanced by captopril in vitro (223). Furthermore, there is no evidence that ACE inhibitors cause any deterioration in asthma, although they do produce a dry cough in some patients, which is unrelated to asthma (602). These kinases are less active against lys-bradykinin than against bradykinin, so that it may have more prolonged effects.

B. Receptors

Kinins activate specific receptors, which have been detected in some tissues using ^{125}I-labeled bradykinin (438), and in intestine, high-affinity binding sites have been found in epithelial cells (147). Using a series of bradykinin fragments and analogs, it has been possible to distinguish two types of receptor; B_1-receptors are selectively activated by lys-bradykinin and des-Arg-bradykinin, whereas B_2-receptors are more potently stimulated by bradykinin itself (483). Selective peptide antagonists have now been synthesized for each receptor type. While most responses to kinins appear to be mediated via B_2-receptors, there is some evidence that B_1-receptors might increase in experimental inflammation (389), and so may be relevant to asthma.

C. Airway Effects

1. Airway smooth muscle. Bradykinin is a potent bronchoconstrictor in guinea pigs in vivo, which is prevented by cyclooxygenase inhibitors (143), and probably mediated by the generation of thromboxane. In humans, both intravenous and inhaled bradykinin causes bronchoconstriction in asthmatic but not in normal subjects (278, 535, 429, 223). In vitro bradykinin has almost no effect on human airways, even in the presence of captopril (223), suggesting that its bronchoconstrictor action is indirect. In contrast to the guinea pig, aspirin does not reduce its bronchoconstrictor effect in human subjects, but cholinergic antagonists partially inhibit the response, suggesting that a vagal reflex mechanism is involved (535, 223). In dogs, bradykinin is a potent stimulant of bronchial C-fibers (316), and in other tissues produces its effects by releasing sensory neuropeptides from capsaicin-sensitive nerves (579). It is possible that bradykinin causes bronchoconstriction in asthmatic patients by a similar action and activates axon reflex mechanisms (43).

There is no evidence that bradykinin causes bronchial hyper-responsiveness in man, since inhalation of bradykinin does not increase responsiveness to other bronchoconstrictor mediators (223), and even reduces the response to histamine, possibly because of release of bronchodilator prostaglandins (223).

2. Vascular effects. Bradykinin is a potent vasodilator of canine bronchial vessels and also increases airway mucosal thickness (333). The effects of bradykinin on vascular smooth muscle may be mediated via prostaglandins, and bradykinin has been shown to release prostacylin also after intravenous infusion in humans (62). Bradykinin also causes microvascular leakage in guinea pig airways (507, 177) and produces a wheal and flare response in human skin (228). Injection of kallikrein into human skin causes a late reaction, suggesting that bradykinin may contribute to this inflammatory response (181), and raises the possibility that it may play a similar role in the late response to allergens in the airways.

3. Airway secretions. Bradykinin is a potent stimulant of ion transport in intestinal mucosa, which may relate to the high density of binding sites (147). Bradykinin also stimulates ion transport across canine tracheal epithelium, and this is inhibited by cyclooxygenase blockade (353). Furthermore, PGE_2 is released from tracheal epithelium by bradykinin.

Less is known about the effects of bradykinin on mucus secretion, although lys-bradykinin (the kinin most likely to be found in gland tissue) stimulates mucus glycoprotein release from canine airways in vitro (38).

4. Effect on nerves. Bradykinin stimulates sensory nerve endings in airways (316) and in human subjects produces pronounced dyspnea (223). This effect is reminiscent of the pain produced by bradykinin application to blister burns in human skin (310). It is possible that bradykinin may therefore contribute to the symptoms of asthma.

D. Role in Asthma

Despite the evidence that kinins are released in experimental inflammation (483), there is little direct evidence that they are involved in asthma. This is because of difficulties of measurement in biological fluids, and because of the lack of specific antagonists for clinical use.

HMWK is consumed during human anaphylaxis (541), suggesting that kinins are produced. Plasma kinins are reported to be increased during asthma attacks (1), but there are considerable doubts about the assay procedures, and the high values reported may represent spontaneous kinin formation in plasma.

Recent studies have demonstrated that allergen challenge leads to production of bradykinin and lys-bradykinin in nasal washings of atopic individuals (476). Furthermore, HMWKs could also be detected together with

albumin (66), suggesting that increased vascular permeability allows entry of HMWK from which kinins are formed by local tissue kallikreins. Such measurements have not been made in the lower respiratory tract, but recently tissue kallikrein has been detected in bronchoalveolar lavage fluid of asthmatic subjects (127).

There are currently no bradykinin antagonists which are suitable for clinical use, but several potent competitive antagonists, which are peptide analogs of bradykinin, have been developed which should prove suitable for animal studies (588).

VII. Adenosine

Recently there has been increasing interest in the possible involvement of the purine nucleoside, adenosine, in asthma, since it may be released by allergen challenge (385) and may cause bronchoconstriction (156).

A. Origin

Adenosine is generated extracellularly by dephosphorylation of AMP by the membrane-associated enzyme 5′-nucleotidase. Adenosine is therefore formed under conditions in which AMP is generated within the cell, such as excessive stimulation or under hypoxic conditions. Adenosine may then be taken up into the cells by facilitated transport (which is specifically blocked by dipyridamole), where it is converted back to AMP or broken down by adenosine deaminase to the inactive inosine. Extracellular adenosine is also rapidly inactivated by adenosine deaminase, and therefore adenosine has a very short duration of action. Thus, the cardiovascular effects of adenosine decay within 1 min of stopping an infusion (226). This suggests that adenosine functions as a local hormone. Adenosine may be released from a variety of cells, including leukocytes (386), and mast cells (395).

B. Receptors

Adenosine interacts with specific cell surface receptors, which either inhibit (A_1) or stimulate (A_2) adenylate cyclase, which may be distinguished by selective agonists (368). Thus, for A_1-receptors, N_6-phenylisopropyl adenosine (PIA) is more potent than N-ethylcarboximide adenosine (NECA), whereas for A_2-receptors, the order of potency is reversed.

While adenosine receptors have been identified in lung by direct receptor binding studies (581), the cellular localization of the receptors is not known, although adenosine appears to be active on a wide range of cells.

C. Actions

When administered by aerosol, adenosine induces rapid bronchoconstriction in asthmatic subjects, but has no effect on normal subjects (156), but the mechanism of bronchoconstriction is not yet certain. Adenosine has little effect on human bronchi in vitro (201), suggesting that the bronchoconstrictor effect is indirect. Pretreatment with an anticholinergic drug does not inhibit the bronchoconstriction (384), suggesting that it is not due to an irritant effect of the inhalation, but it is inhibited by cromolyn, raising the possibility that mediator release may be important (155). Adenosine is known to enhance the release of histamine from human lung mast cells under certain conditions (288), and in rodent mast cells selectively enhances the secretion of histamine, rather than that of newly formed mediators (395). The H_1-antagonist, terfenadine, markedly inhibits the bronchoconstriction to inhaled AMP (which is converted to adenosine) (477), suggesting that the bronchoconstrictor effect of adenosine in asthma may be due to selective release of histamine from airway mast cells. The adenosine receptor mediating bronchoconstriction paradoxically appears to be the A_2-receptor, since NECA is more potent than PIA in causing bronchoconstriction in rats in vivo (455), and presumably this receptor is localized to airway mast cells.

Another effect of adenosine on airway smooth muscle which has recently received attention is its effect on beta-adrenoceptors. Adenosine appears to enhance beta-receptor tachyphylaxis in airway smooth muscle (399) through the A_1-receptors.

The effect of adenosine on airway secretions and other target cells of the airway has not been investigated.

D. Role in Asthma

After allergen challenge, plasma concentrations of adenosine increase in asthmatics in parallel with bronchoconstriction, but no increase is seen after similar bronchoconstriction induced by methacholine (385). The increase in plasma concentrations is unexpected, since the half-life of adenosine is so short, and may suggest that adenosine is generated secondarily from other cells.

Theophylline, at concentrations which are within the therapeutic range (55 to 110 μM), is an antagonist of adenosine receptors, and its anti-asthma effects have, therefore, been ascribed to adenosine antagonism (214). Theophylline selectively inhibits the bronchoconstrictor action of inhaled adenosine (157), but it is unlikely that its anti-asthma effects are due to adenosine antagonism, since a related methylxanthine, enprofylline, has even more potent bronchodilator effects, but is not an effective antagonist of adenosine receptors (460). Thus, theophylline cannot be used as a probe to examine the role of endogenous adenosine in asthma, since it has many other effects (44). Until specific adenosine antagonists, which do not have other actions, can be used clinically, the role of adenosine in asthma remains difficult to evaluate.

VIII. Sensory Neuropeptides

Recently there has been considerable interest in the possible involvement of axon reflex mechanisms and the role of sensory neuropeptides in airway pathophysiology (43, 45, 46, 375, 376). These sensory neuropeptides are

proinflammatory and may be involved in neurogenic inflammation and exaggerating the inflammatory response in asthmatic airways. Several neuropeptides have now been localized to sensory nerves, including the tachykinins substance P (SP), neurokinin A (NKA, previously known as substance K), and neuropeptide K (NPK), as well as calcitonin gene-related peptide (CGRP). Neurokinin B (NKB, previously known as neuromedin L) has not yet been identified in lung.

A. Origin

Sensitive neuropeptides are localized to capsaicin-sensitive C-fiber afferents in airways. The peptides are synthesized in sensory neurones in the nodose and jugular ganglia and transported peripherally (376). There may also be sensory neuropeptides in nerves which originate within the airway itself. Histochemical studies have demonstrated that SP immunoreactivity is localized to fine nerves within and beneath airway epithelium, around blood vessels and ganglia and, to a lesser extent, within airway smooth muscle (372). These nerves may be found peripherally as well as centrally. SP-immunoreactive nerves are less numerous in human airways (372) and, in some studies, have not been convincingly demonstrated (332). However, rapid degradation of SP in airways, and the fact that SP may decrease with age and possibly with smoking, might explain the difficulty in demonstrating this peptide in lungs obtained at surgical resection.

NKA is coded by the same gene as SP (426) and is therefore colocalized within sensory nerves (287). CGRP is frequently colocalized with tachykinins, and CGRP-immunoreactive nerves have been demonstrated in human airways (447). In some animal species, CGRP is also localized to neuroendocrine cells in the airway.

Sensory neuropeptides are released by capsaicin from sensory nerve endings by a calcium-dependent mechanism, and this has recently been demonstrated in isolated perfused guinea pig lungs (508). Agents that activate sensory nerves, such as bradykinin, have also been shown to induce the release of sensory neuropeptides from lung (508).

Less is known about the metabolism of sensory neuropeptides, but it seems likely that tachykinins are rapidly degraded by peptidases. In guinea pig lung strips, SP causes contraction only in the presence of captopril, suggesting that, in this preparation, metabolism by ACE is critical (603) and, in vivo, captopril enhances the bronchoconstrictor effect of SP (529). Neutral metalloendopeptidase (enkephalinase) may be a more important degrading enzyme in airways, and inhibition by thiorphan or phosphoramidon greatly enhances the airway effects of SP in animals (529, 88) and in human airways (218). CGRP is presumed to be more slowly metabolized, since its effects may be very prolonged (91), and degradative products may have vasodilator activity. CGRP may inhibit the breakdown of SP (352) and may, therefore, directly potentiate its effect (90).

B. Receptors

At least 3 receptor subtypes for tachykinins have now been recognized (105, 340). NK_1 receptors (previously known as SP-P receptors) are selectively activated by SP, NK_2 (previously SP-E) receptors by NKA, and NK_3 (previously SP-N) receptors by NKB. This suggests that, although different tachykinins may be released from the same nerves, they may regulate different physiological functions, as discussed below for airway effects. Using the autoradiographic approach, SP receptor distribution has been studied in guinea pig and human lung (113). SP receptors are predominantly localized to smooth muscle of airway cells from trachea down to terminal bronchioles, with less labeling of epithelial cells. In human airways, submucosal glands were also labeled (48). Surprisingly, labeled NKA does not show significant localization to guinea pig trachea (601). As in other organs, tachykinins stimulate PI turnover in airway smooth muscle and, in keeping with functional data, NKA is more potent than SP in this respect (251).

CGRP binds to specific receptors which have been identified in several peripheral organs, including lung (424). Recently the distribution of CGRP receptors has been determined in guinea pig and human lung using autoradiography. In airways, CGRP binding sites are localized predominantly to bronchial vessels, with only scanty labeling of airway smooth muscle and epithelium in both species (383).

C. Airway Effects

1. *Airway smooth muscle.* In animals, tachykinins produce bronchoconstriction both in vitro and in vivo (375). Since tachykinin receptors are found even on terminal bronchioles, this suggests that tachykinins may regulate bronchomotor tone in peripheral airways (113), and this is confirmed by functional studies (218). SP contracts human bronchi in vitro (373), but NKA is significantly more potent, suggesting an NK_2 receptor on human airway smooth muscle (397, 446). Neuropeptide K is also a potent bronchoconstrictor in animals (287) and contracts human airways in vitro (397). Infusion of SP in human subjects has profound cardiovascular effects but little effect on airway function with a small bronchoconstrictor effect, followed by bronchodilatation at higher infusion doses. This may reflect reduced vagal tone resulting from systemic vasodilatation (227). Even given by inhalation, SP has no significant effect on airway function in subjects with mild asthma who are hyperresponsive to histamine (227). This could be due to enzymatic degradation of SP in the airway. NKA has less marked cardiovascular effects than SP, but causes bronchoconstriction at higher infused doses (193) and is reported to cause bronchoconstriction when given by inhalation to asthmatic subjects (305).

There is now considerable evidence that tachykinins released from sensory nerves can account for nonadrenergic, noncholinergic (NANC) bronchoconstriction after vagal stimulation in rodents (18). Capsaicin, which releases sensory neuropeptides, also causes bronchoconstriction in these species, and chronic treatment with capsaicin, which depletes sensory neuropeptides, results in loss of NANC bronchoconstriction (376). In human airways, capsaicin also causes contraction in vitro, suggesting that it is releasing sensory neuropeptides (373). In vivo inhaled capsaicin causes intense coughing in human subjects, but only transient bronchoconstriction which is prevented by anticholinergic treatment, suggesting a vagal reflex rather than release of sensory neuropeptides (222).

Tachykinins, while having a direct effect on receptors in airway smooth muscle, may also produce bronchoconstriction indirectly. Thus, in rabbits, the bronchoconstrictor response is inhibited by atropine, suggesting release of acetylcholine from cholinergic nerves (565). A similar effect is seen in guinea pig airways, where a facilitating action on postganglionic cholinergic nerves, rather than preganglionic, has been found (60). However, similar studies have not shown such an effect on human airways in vitro (K. Rhoden and P. J. Barnes, unpublished results). Epithelial removal markedly enhances the contractile effect of tachykinins in guinea pig airways, which might be explained either by loss of "epithelium-derived relaxant factor" (EpDRF) or removal of metabolizing enzymes, since phosphoramidon eliminates the effect of epithelial removal (251, 219).

2. Secretion. SP is one of the most potent known stimulants of mucus secretion in animal airways (38, 141). Similarly, in human airways in vitro, SP is an effective stimulant of mucus secretion (56), which correlates with the demonstration of SP-receptors on human airway submucosal glands (113).

Tachykinins also transiently increase conductance across canine airway epithelium and, since SP is more potent than neurokinins, this suggests that an NK_1 receptor is involved (480). In the guinea pig, the effect of epithelial removal is also greater for the bronchoconstrictor effect of SP than for NKA, suggesting that NK_1 receptors may be important in the epithelial modulation of airway smooth muscle tone (251). Whether this is also true for human airways is not yet certain. The effect of CGRP on airway secretion is also unknown, but, since CGRP is a potent vasodilator, the increase in blood flow to airway glands might be expected to increase secretion.

3. Vascular effects. SP is a potent systemic vasodilator in human subjects (227), and in animals it increases bronchial flow (333). SP also causes microvascular leakage in guinea pig airways (507) and is more potent than NKA and NKB (34), suggesting that an NK_1 receptor is involved. In animals treated with capsaicin, mechanical trauma and cigarette smoke no longer cause microvascular leakage in rodents, indicating that release of sensory peptides is involved in this response (374). It is not possible to study airway microvascular leakage in humans, but, in skin, SP causes a wheal and flare response, suggesting vasodilatation and increased vascular permeability (256). As in guinea pig airways, SP is more potent than NKA or NKB in this respect (221).

CGRP is a very potent vasodilator in human skin, but produces a wheal only at very high doses (91, 221). In guinea pig airways, CGRP does produce microvascular leakage (34), but presumably is a bronchial vasodilator in both guinea pig and human airways since a very high density of CGRP-receptors is localized to bronchial vessels (383). Since CGRP is a vasodilator and SP increases leakage, it is possible that they may interact synergistically if released together. Potentiation of SP-induced leakage with CGRP has been reported in guinea pig and rabbit skin (229, 90), but not convincingly in human skin (54). No potentiation of SP induced leak by CGRP in guinea pig airways has been found (34), possibly because bronchial blood flow is already high and cannot be further potentiated.

4. Inflammatory cells. The SP-induced wheal and flare response in human skin is inhibited by antihistamines (212) and increases the release of histamine into draining veins (50). This suggests that SP degranulates mast cells in human skin, but there is no direct evidence that this is so in human airway mast cells. Furthermore, intradermal capsaicin, which produces a flare in human skin, does not cause a wheal in the same way as antigen (50), suggesting that release of endogenous sensory neuropeptides may not degranulate mast cells. The effect of SP on mast cells may not be mediated by a classical SP-receptor (212), but may be due to the basic nature of this peptide.

SP may also have effects on neutrophils and lymphocytes and may, therefore, be involved in regulation of inflammatory reactions (457), although there is no direct evidence for this in airways.

D. Role in Asthma

Although sensory neuropeptides have several effects which might indicate a role in asthma (45), direct evidence for their involvement is lacking, since there are no specific antagonists which are suitable for clinical use. In rodents sensory neuropeptides may mediate NANC bronchoconstriction and airway vascular leakage after vagal stimulation, as discussed above. Furthermore, stimulation of sensory nerves by inflammatory mediators causes release of sensory neuropeptides from lung (508). Neurogenic inflammation and axon reflex mechanisms are well documented in the skin (459), axon reflexes are involved in the skin response to antigen (377), and it is possible that similar axon reflex mechanisms may operate in the airways in asthma (43). SP- and CGRP-immunoreactive nerves are certainly present in human airways (372, 447) and might, therefore, be released by

an axon reflex in asthma, since airway epithelium is damaged and sensory nerve endings may be exposed (331). Inflammatory mediators, such as bradykinin, may release sensory neuropeptides, as discussed above. Axon reflex mechanisms might, therefore amplify inflammation in asthmatic airways, leading to exaggerated bronchoconstriction and mucosal edema. Although no selective tachykinin antagonists are yet available for clinical use, it might be possible to study the contribution of axon reflex mechanisms by inhibitory release of sensory neuropeptides. In the guinea pig, clonidine inhibits NANC and cholinergic vagal bronchoconstriction via prejunctional alpha$_2$ receptors (17), and opioids selectively inhibit NANC bronchoconstriction both in vitro (217) and in vivo (71), acting via μ-opioid receptors on sensory nerves. Depletion of airway sensory neuropeptides by capsaicin does not alter base-line bronchial responsiveness in animals (569). Capsaicin pretreatment of guinea pigs has been reported to inhibit bronchial hyper-responsiveness induced by toluene diisocyanate, by mechanisms that remain to be explored (569); however, it is likely that the measurement of airways resistance mainly reflects changes in nasal resistance. The edema induced by cigarette smoke in guinea pig nasal mucosa is inhibited by capsaicin pretreatment (374), indicating that sensory neuropeptides are involved in the airway inflammatory response to irritants.

IX. Complement

Over 100 yr ago, it was recognized that serum contained soluble and heat-labile proteins which could lyse bacterial cells. It is now apparent that the complement cascade represents a complex system consisting of a range of plasma proteins that play a role in host defense and in a number of pathological disorders of both immunological and nonimmunological origin. The activation sequence and generation of the various components are complex (100), and we have concentrated on the involvement of two complement components, C3a and C5a (anaphylatoxins), which have documented airway effects.

A. Origin and metabolism

The anaphylatoxins are fragments of the complement cascade that play little part in the further activation of the cascade itself, although they may regulate the further production of the C2 component, but may have inflammatory effects. C3a and C5a are generated following activation of the complement pathway by both the classical and the alternative pathways. The complete amino acid sequence of the anaphylatoxins has now been elucidated in several species, including man, and there is considerable homology. C5a has 74 amino acids and contains an oligosaccharide attached at position 64 with the active site being the carboxy-terminal pentapeptide Met–Glu–Leu–Gly–Arg. The remainder of the molecule is required for functional binding to the C5a receptor, which is not so with C3a, although the carboxyterminal of this molecule is again the active site. C3a has 77 amino acids with the carboxy-terminal pentapeptide Leu–Gly–Leu–Ala–Arg.

The anaphylatoxins are rapidly inactivated in plasma by the so-called anaphylatoxin inactivator (AI) which expresses a carboxypeptidase B function removing the C-terminal arginine, leaving C3a des Arg and C5a des Arg, products devoid of much of the biological activity of the anaphylatoxins C3a and C5a, although still retaining chemotactic activity. Until the recent development of carboxy-peptidase inhibitors, the in vivo levels of anaphylatoxins have been difficult to measure.

B. Receptors

Specific membrane receptors have been identified which bind C3 and its various components. C3a receptors have been identified on leukocytes and mast cells, while C5a receptors have been identified on mast cells, monocytes, platelets, and leukocytes (482). To date, specific receptors for anaphylatoxins have not been demonstrated in airway preparations, but C5a is able to contract bronchial smooth muscle preparations in vitro (482).

1. Smooth muscle contraction. Intravenous injection of guinea pigs with C5a causes bronchoconstriction (85), but the mechanisms involved are unknown, although C5a and C5a des Arg induce the release of histamine (498, 503), prostaglandins (504), and leukotrienes (554) from guinea pig lung. C5a elicits airway smooth muscle contraction in both perfused guinea pig lungs (503) and isolated tracheal smooth muscle preparations (482), independently of histamine release. The precise contribution of arachidonic acid metabolites to C5a-induced bronchoconstriction is not clear, although both cyclooxygenase and lipoxygenase metabolites inhibit C5a-induced contraction of airway smooth muscle preparations. C3a is a less potent inducer of airway smooth muscle contraction than C5a in the guinea pig (555). This effect appears to be mediated predominantly via a cyclooxygenase product, despite the release of histamine (555). Both C3a and C5a induce marked tachyphylaxis in airway smooth muscle preparations, although there is no cross-desensitization between them, indicating that they are likely to activate discrete receptors (482).

2. Vascular effects. Complement activation has long been recognized as a trigger of increased vascular permeability in skin, which was believed to be secondary to histamine release (175). C5a and C3a induce vascular permeability through neutrophil activation, although the role of the neutrophil has not been fully elucidated (604). Although C5a releases PAF from neutrophils (605), it is unlikely that PAF is the mediator responsible for the neutrophil-dependent vascular permeability induced by C5a as PAF antagonists do not inhibit C5a-induced edema formation (273). In man, C5a produces immediate wheal and flare reactions in skin; an H1-antihistamine reduced the flare response but not the wheal (613); in

addition, biopsies of skin showed neutrophil infiltration, endothelial cell edema, and mast cell degranulation. There is little work in the role of C5a in airways, although preliminary studies have shown that C5a is associated with neutrophil recruitment in airways (300).

3. Mucus secretion. Little is known about the effects of the anaphylatoxins on airway secretion or mucociliary clearance. C3a stimulates mucus glycoprotein secretion from human airways in vitro (393a), probably via a direct effect on secretory cells.

4. Chemotaxis and cell activation. One of the most widely studied effects of anaphylatoxins is their ability to induce activation of inflammatory cells. C5a and C5a des Arg have chemotactic activity for neutrophils, with a potency even greater than that of LTB4 (417). C5a also has chemotactic activity for macrophages (486), basophils (319), and eosinophils (318). In contrast, human C3a is devoid of chemotactic activity (200). Both C5a and C5a des Arg also stimulate the adhesion of inflammatory cells and elicit the release of other mediators, including lysosomal enzymes (401), free oxygen radicals (72), both lipoxygenase and cyclooxygenase products of arachidonic acid metabolism (136), and PAF from both neutrophils (110) and eosinophils (344).

5. Bronchial hyper-responsiveness. Inhalation of C5a des Arg causes increased airway responsiveness to histamine 4 h later (300), at a time when neutrophil infiltration occurs in the airways. The increased airway responsiveness is reduced in animals rendered neutropenic, suggesting that neutrophils contribute to the induction of bronchial hyper-responsiveness by C5a.

D. Role in Asthma

Little is known of the role of anaphylatoxins in human asthma, since studies with inhibitors of complement activation have not yet been reported in man. Measurement of C5a and C3a have proved to be difficult in plasma, and their release has not yet been demonstrated in asthma. The potent effects of these mediators on microvascular leakage and bronchial smooth muscle have not been confirmed in human subjects, and no specific antagonists are available. Several clinical investigations have reported the activation of the complement cascade during asthma. Plasma C4 concentrations have been found to be elevated in childhood asthma and depressed in non-atopic adult asthmatics (321), although other investigators have not confirmed this observation (263, 236, 574, 176). Furthermore, no changes in complement are detected in allergic asthmatics following either early or late reactions to allergen provocation (293, 315, 12). A few patients develop reduced hemolytic complement activity or C4 in arterial or venous blood following allergen provocation (548), whereas others have reported an increase (65). The role of complement in aspirin-sensitive asthma is equally controversial, since some investigators have reported decreased complement levels after oral challenge with aspirin (28), whereas others report changes in hemolytic complement activity or C4 in arterial or venous blood following aspirin provocation (472). These studies do not exclude the possibility that there may be local complement activation within the airways in asthma. The use of specific inhibitors of the complement cascade, such as N-acetyl-aspartyl-glutamic acid (NAAGA), may be useful in asthma, and preliminary results have already indicated a beneficial effect in allergic rhinitis (233).

X. Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) was once considered to be an important mediator of asthma, since it caused bronchoconstriction in several animal species, but its relevance to human asthma now seems doubtful.

A. Origin

Serotonin is formed by decarboxylation of tryptophan in the diet and stored in secretory granules. In rodents, serotonin is present in mast cell granules, but this is not the case in humans. Serotonin in man is localized to neuroendocrine cells of the gastrointestinal and respiratory tract, to certain nerves, and to secretory granules in platelets. The possible involvement in platelets in asthma (416) has, therefore, reawakened interest in serotonin.

B. Receptors

The development of specific antagonists has made it possible to recognize at least three types of serotonin receptor. 5-HT_1-receptors are usually inhibitory, 5-HT_2-receptors are excitatory and mediate smooth muscle contraction, and 5-HT_3-receptors are present on nerves and stimulate neurotransmitter release from certain peripheral nerves (487). The development of more and more selective antagonists has provided evidence for heterogeneity within 5-HT_1- and 5-HT_3-receptor subtypes.

C. Airway Effects

Serotonin causes bronchoconstriction in several species, including the guinea pig, cat, rat, dog, and monkey; but there is considerable doubt about its effect in human airways. Serotonin even relaxes human airways in vitro (479). In vivo inhaled serotonin was reported to cause bronchoconstriction in some asthmatic patients (448), but other studies have found no consistent bronchoconstrictor response in either normal or asthmatic subjects (573, 158).

In dogs, serotonin enhances vagal nerve but not acetylcholine-induced bronchoconstriction, suggesting that it may facilitate release of acetylcholine from airway nerves (257, 525). Whether this occurs in human airways has not been determined.

Serotonin is a potent constrictor of human pulmonary vessels (479), but it is not known whether it constricts bronchial vessels. It also causes microvascular leakage in

guinea pig airways (507) and could have a similar effect in man since it causes a wheal response in human skin and stimulates an axon reflex (487).

Few studies have been performed with antagonists of serotonin in asthma. Ketanserin, a 5-HT_2 antagonist, has no protective action against exercise-induced asthma (544).

XI. Chemotactic Factors

Many of the mediators discussed above, and particularly LTB_4, 15-HETE, PAF, and C5a, have potent chemotactic activity. In addition, a number of poorly defined large molecules have been identified as chemoattractants and investigated for their potential contribution to allergic inflammation. However, almost all the work in this area has relied upon in vitro observations of chemoattractant activity, and no conclusive proof of the involvement of these materials in vivo has been obtained. Materials displaying chemotactic activity by neutrophils in vitro have been identified as products released from human leukemic basophils (363), rat mast cells (565), and extracts of lung tissue (437). Neutrophil chemotactic activity has also been detected in the serum of patients undergoing experimentally induced physical and temperature-induced urticaria (600, 32), allergic and nonallergic bronchoconstriction (546, 30). However, many of the defined low-molecular-weight chemotactic factors (e.g., LTB_4 and PAF) avidly bind to plasma proteins, and it still remains plausible that such chemotactic activity could be secondary to these low-molecular-weight materials bound to plasma proteins. Neutrophil chemotactic activity cannot be attributed to the complement fragments C3 or C5 as a high-molecular-weight, heat-stable protein (M_r ~600,000) having neutrophil chemotactic activity (NCA) has been shown to be unaffected by preincubation with an antibody to human C3 or C5 complement fragments (347). NCA is released in a variety of inflammatory conditions, including urticaria (600, 32), and following challenge of asthmatics by exercise (347) or with an appropriate antigen (31, 422). However, the specificity of this molecule as a marker of allergic responses is highly dubious, because similar NCA chemotactic activity has been reported in patients with active bronchitis and pneumonia (152). It seems likely that NCA may represent an indication that an acute inflammatory process has taken place in much the same way as acute plasma proteins are utilized.

Another problem with the various NCA activities described experimentally and clinically is that they rely on the use of a bioassay based on movement of neutrophils in vitro and, as such, all current measurements of NCA merely reflect a general activity rather than a defined chemical entity. As mentioned earlier, until specific chemical quantification of the proposed NCA activities is developed, all such chemotactic activity could be attributed to the release of low-molecular-weight molecules binding to plasma proteins.

A second group of chemotactic factors have also been described that share the property of being selective for eosinophils (318). Eosinophil chemotactic factor of anaphylaxis (ECF-A) has been identified in supernatants from IgE-challenged tissue extracts of human lung (320) and isolated cell preparations, such as human leukemic basophils (363) and human mast cells (30). Furthermore, ECF activity has been identified in the serum of patients undergoing antigen-induced bronchoconstriction (406) and with urticarias produced by physical challenge (600). ECF-A was originally described as two tetrapeptides, having the sequence Val–Gly–Ser–Glu and Ala–Gly–Ser–Glu (237), but it is now clear that such tetrapeptides only form a very small component of the original ECF-A (599). ECF-A is far less potent than PAF as a chemotactic agent from human eosinophils, however (597).

XII. Oxygen Radicals

Oxygen radicals are generated as part of the inflammatory reaction and are therefore likely to be involved in the pathophysiology of asthma. Activation of various inflammatory cells, including macrophages, neutrophils, eosinophils, and mast cells, generates the oxygen intermediates superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) (36); the hydroxyl radical ($OH^{\cdot}$) is formed nonenzymatically as a secondary reaction. Oxygen radicals may have various toxic effects on cellular function, including inhibition of certain enzymes (especially those dependent on SH groups), damage to DNA, and the formation of lipid peroxides from the polyunsaturated fatty acids present in the cell membrane (311). It is surprising that so little is known about the effects of oxygen radicals on airway function.

Oxygen radicals have effects on airway smooth muscle in vitro. H_2O_2 is the oxygen radical which appears to have the major effect on airway tone and causes contraction both in bovine (552) and guinea pig airways (61). In the guinea pig, the contractile effect of H_2O_2 is greatly enhanced by removal of epithelium, suggesting that oxygen radicals release a relaxant factor. The bronchoconstriction is also reduced by indomethacin, suggesting that H_2O_2 also releases constrictor cyclooxygenase products (61). Oxygen radicals may also affect airway smooth muscle by an action on beta-adrenoceptor function. Thus, alveolar macrophages incubated with guinea pig trachea lead to reduced relaxation responses to isoproterenol, an effect which is prevented by free radical scavengers (189). However, direct incubation of oxygen radicals with airways fails to alter beta-receptor function (61).

Oxygen radicals may also have potent vascular effects. H_2O_2 potently relaxes pulmonary vascular smooth muscle in vitro (253) and also causes increased vascular permeability, possibly via a direct basic effect to vascular endothelial cells (170). It is therefore possible that oxygen radicals might contribute to the hyperemia and edema in asthmatic airways.

The role of oxygen-derived free radicals in asthma is still not certain, but perhaps studies using antioxidants or free radical scavengers might show some benefit. Ascorbic acid is an effective antioxidant and reduces methacholine-induced bronchoconstriction in asthmatic subjects (410), although this could be mediated through an alternative mechanism.

XIII. Conclusions

Many different mediators have now been implicated in asthma, and we have discussed the evidence for their involvement in asthma. In most cases the evidence is circumstantial, and it will be necessary to develop more potent and selective antagonists before the role of each mediator in a complex inflammatory disease, such as asthma, can be elucidated. There is increasing evidence that there are complex interactions between mediators with amplification or modification of their effects, which may make it even more difficult to determine the contribution of a single mediator. The therapeutic implication is that an antagonist of a single mediator is unlikely to have a major clinical effect. Thus, even potent antihistamines have not proved to be effective in the management of clinical asthma. Perhaps PAF might prove to be the exception, since this mediator most closely mimics the pathological features of asthma, and the imminent availability of specific PAF antagonists for clinical studies should shortly answer this question. It seems likely that other mediators will be described in the future and may contribute to the inflammatory reaction of asthma.

We have emphasized human studies where possible, since there appear to be marked differences between species in production of and response to inflammatory mediators. Furthermore, there is no animal model which duplicates all the features of human asthma, although animal studies have provided important information about the processes involved in asthma, such as microvascular leakage, which cannot yet be measured in human airways. In the future, there should be greater emphasis on human studies, and particularly studies in asthmatic patients, in order to unravel the complexities of the inflammatory response and the contribution of different mediators.

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