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The role of increased airway microvascular permeability and plasma exudation in asthma

K.F. Chung, D.F. Rogers, P.J. Barnes, T.W. Evans

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ABSTRACT: Airway oedema and inflammation are recognized as cardinal features of asthma, resulting from increase microvascular permeability of the bronchial circulation with the exudation of plasma and inflammatory cells into the airway lumen. Resistance to airflow is increased and the epithelium is disrupted either directly or by cytotoxic proteins derived from migrating inflammatory cells. Such mediators include bradykinin, platelet-activating factor (PAF), leukotrienes and histamine. Antigen-induced and neurogenic inflammation, generated by immunoglobulin E (IgE) and neuropeptides respectively, may also contribute to oedema generation. Assessment of increased bronchial vascular permeability in animals has largely involved measurement of the extravasation of radiolabelled albumin or protein-bound dyes. Non-invasive techniques are less reliable in humans, but measurement of the rate of clearance of inhaled particles labelled with isotope may prove successful. Airway oedema appears to be an important feature of asthma and future research may be aimed at developing drugs that specifically prevent airway microvascular leakage.

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Dept of Thoracic Medicine, National Heart and Lung Institute, Dovehouse Street, London, UK.

Correspondence: Dr T.W. Evans, Brompton Hospital, Fulham Road, London SW3 6HP, UK.

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Airway oedema is a prominent feature of patients who have died in status asthmaticus [1, 2]. An accompanying feature is the presence of exudated plasma in the interstitium of the airway wall as well as in the lumen, both of which may be responsible for the shedding of ciliated epithelial cells which is histologically characteristic of asthma [1]. Increased microvascular permeability is one of the cardinal signs of the inflammatory process [3] and its importance in the pathophysiology of asthma has become increasingly apparent with the accumulation of new information on the physiological and pharmacological control of airway microvasculature [4, 5]. Although the bronchial circulation receives only 1–2% of total cardiac output, recent studies of the anatomical distribution of the bronchial microcirculation in casts of human airways reveal the presence of abundant capillary-venular plexuses in the submucosal layer [6]. These histological studies indicate the potential importance of the vascular network in the airways. Whether or not the venular endothelial junctions in the airways of asthmatic subjects are abnormally leaky is unknown. However, they do respond to many of the inflammatory mediators that are implicated in the pathogenesis of asthma [7]. In this review, the potential mechanisms and effects of increased airway microvascular permeability will be considered and the effects of pharmacological agents discussed, particularly in relation to the treatment of asthma.

Effects of plasma exudation

Airway mechanics

In humans, local instillation of antigen onto the bronchial mucosa of asthmatic subjects causes acute swelling and narrowing of the airways which can be directly visualized through a bronchoscope [8, 9]. The response is rapid in onset, resolves slowly and could represent airway mucosal oedema secondary to increased microvascular leakage. The duration of swelling is possibly dependent on the removal of exuded fluid by bronchial lymphatics, or its passage into the airway lumen. Very little information is available on the role of airway lymphatics in such circumstances due to the technical difficulties in studying their physiology. Secondly, re-entry of exuded fluid into the vascular compartment may occur, although there is no evidence for this. The precise degree to which measurements of airway resistance reflect smooth muscle contraction or acute inflammation after inhalation of a mediator is not known, although there is indirect evidence to suggest that oedema contributes significantly to increased resistance.

For example, platelet-activating factor (PAF) causes airway narrowing that is only partly inhibited by a dose of beta-agonist which completely prevents methacholine-induced bronchoconstriction [10]. Because PAF has little

direct contractile effect on airway smooth muscle *in vitro*, but has been shown to increase plasma exudation from bronchial vessels [11, 12], the partial inhibition may be due to airway oedema which is unaffected by beta-agonists. In addition to basement membrane thickening, smooth muscle hypertrophy and intraluminal mucus, airway oedema is one of the features of asthma which may underlie the enhanced airway responsiveness to endogenous and exogenous bronchoconstrictor mediators [13]. Small increases in wall thickness due to oedema which do not lead to changes in baseline lung function may, theoretically, significantly increase airflow resistance [14, 15].

Epithelial changes

The epithelium is being increasingly recognized as playing an important role in the maintenance of airway homeostasis [16]. In asthma, the epithelium is damaged [1, 17], although the mechanisms by which this occurs remain unclear. Plasma exuded into the airway interstitium may increase hydrostatic pressure and physically disrupt the epithelium. Cytotoxic proteins derived from migrating eosinophils [18] may also damage epithelial cells directly. The significance of transudation of plasma, in addition to inflammatory cells, into the airway lumen through the damaged epithelium is becoming increasingly apparent.

Proteinaceous mucous plugs are found in the airways of asthmatics [1] and their sputum contains elevated levels of plasma proteins when compared to control subjects, even when the disease is relatively mild [9, 19, 20]. Plasma proteins may increase the viscosity and quantity [21, 22] of airway mucus leading to decreased mucociliary clearance [23]. Indeed, increased airway microvascular permeability by agents such as PAF administered *via* the trachea or intravenously [24, 25], capsaicin (which stimulates the release of tachykinins such as substance P) and antigen in sensitized animals [25, 26] have been associated with an increase in luminal protein recovery, which is indicative of increased airway epithelial permeability.

The mechanism underlying this coincidence of increased airway epithelial and venular endothelial permeabilities is unclear. It is possible that mediators affect both barriers simultaneously and comparisons of results following their administration *via* the intravenous or endotracheal routes might resolve this point. Secondly, increased epithelial permeability may result from the extravasation of plasma into the bronchial interstitium after an increase in endothelial permeability. The mechanisms of epithelial permeability changes have not been established, but it seems clear that increased epithelial permeability to molecules such as albumin is not invariably accompanied by epithelial damage.

Generation of mediators

Increased kallikrein activity, possibly secondary to plasma exudation, has been found in bronchoalveolar lavage fluid from asthmatics and may result in increased bradykinin generation [27]. Bradykinin has been shown to stimulate bronchial C-fibre sensory nerve endings in dogs [28]. Damage to the airway epithelium in asthma may result in exposure of these nerve terminals which would then be stimulated by bradykinin [29]. Consequent activation of local axon reflexes, with antidromic conduction down the collateral nerve fibres, has been proposed as a mechanism for development of neurogenic inflammation with plasma exudation [30]. Other mediators may also be generated from exuded plasma and inflammatory cells. Although complement activation has not been detected in the circulation of asthmatics during acute attacks or after allergen challenge [31], it may occur locally in airway tissue following increased bronchial microvascular permeability leading to a potentiation of airway inflammatory responses. However, there is a lack of data as to whether significant amounts of both complement fragments and kinins are generated in the inflammed airways of asthmatics.

Measurement of airway microvascular permeability

Animals

Methods for measuring airway microvascular permeability are usually invasive and rely on the extravasation of intravascular albumin. In animals, SARIA and LUNDBERG [32, 33] made use of Evans blue dye, used previously in skin [33], to assess the extravasation of macromolecules in the airways quantitatively. Evans blue binds to serum albumin when injected intravenously and spectrophotometric measurement of the quantity of dye extractable from airway tissue has been used as an index of increased microvascular permeability. In skin, this index correlates well with extravasation of radio-labelled albumin when cutaneous microvascular permeability is increased using histamine [34]. A similar correlation is found in the airways (Rogers et al. J. Pharmacol. Methods, 1989, 21, 309–315). One advantage of the method is that measurement of regional changes in microvascular permeability at different anatomical levels of the airways is possible, in addition to localization of the tissue distribution of dye using fluorescence light microscopy [33]. However, with this method the site of dye extravasation cannot be determined precisely because Evans blue is a highly diffusible molecule and once in the interstitium may dissociate from albumin and diffuse back into the vascular space. In addition, the role of other factors such as lymphatic clearance and reabsorption into the vascular space is unknown. Monastral blue, a copper phthalocyanine pigment with a particle size of approximately 200 nm, also crosses areas of increased microvascular permeability and is subsequently trapped in the basal lamina [35]. Because of its electron density, Monastral blue can be used to localize the site of increased microvascular permeability. Indian ink particles share similar properties and have been used to examine airway microvascular leakage in guinea-pigs [11]. There are currently no

comparative data between the Evans blue and Monastral blue techniques, but the former suffers from the disadvantage of occasionally showing high baseline values, possibly reflecting the effects of surgical procedures (such as exposing a vein in the neck) on permeability.

Extravasation of the macromolecular tracer fluorescein iso-thiocyanate dextran (FITC-dextran) which has a molecular weight similar to that of albumin, but a larger radius (60Å), can be visualized directly under fluorescence microscopy and the number of leakage sites counted [36]. BJUEFALT *et al.* [37] have quantified the content of extravasated FITC-dextran in excised airway tissue in guinea-pigs as a measure of vascular leakage and also accounted for the blood pool content using technetium-labelled erythrocytes. This technique required no surgical dissection, but the guinea-pig had to be intubated to enable the intratracheal administration of test agents. The approach appeared to be sensitive, as surgical procedures such as dissection of the neck to expose the vagi caused significant extravasation of FITC-dextran. In addition, measurement of albumin in the airway secretions obtained through the endotracheal tube provides a measure of airway epithelial permeability. The method therefore provides simultaneous assessment of endothelial and epithelial permeability and the time-course of events. WOODWARD *et al.* [38] examined the extravasation of ^{125}Iodine-labelled bovine serum albumin in guinea-pig trachea *in vivo* and measured blood volume using ^{51}Cr-labelled erythrocytes and expressed their results as extravascular albumin per g dry weight of trachea.

Direct assessment of airway oedema is more difficult. Fixation and dehydration affect the degree of oedema. Rapid freezing techniques have been used to demonstrate bronchovascular "cuffs" of fluid in pulmonary oedema [39], but have not been applied to the airways. Measurement of wet to dry weight ratios is possible, but may be insensitive [40, 26]. Direct visualization of airway oedema by endoscopy following local instillation of antigen in asthmatic subjects has been reported [8, 9], but quantification of the response is difficult. In an open tracheal preparation in the dog, rapid changes in mucosal thickness have been recorded using a probe to touch the mucosal surface after administration of vasoactive agents into the tracheal circulation [41]. The changes were of short duration and probably reflect changes in bronchial blood flow rather than the accumulation of extravascular fluid.

Humans

Direct measurement of airway microvascular permeability is difficult and information about mechanisms and control of the bronchial microvasculature has been obtained largely from animal experiments. Methods that can be used in intact man are clearly required for the study of plasma exudation in the lower airways. Recent studies have examined the rate of transfer of inhaled ^{99m}Tc-labelled diethylenetriamine pente-acetate (DTPA), a small molecule of 492 daltons, into blood as a measure of epithelial "permeability". Thus, bronchial clearance of DTPA has been found to be increased in smokers but not in asthmatic subjects [42, 43]. However, the site of "permeability" measured by this method is unclear and may be the vascular or mucosal epithelium [44]. The reported increase in DTPA clearance in asthmatics after histamine inhalation [45, 46] may, therefore, not reflect increased airway microvascular permeability. The penetration of inhaled solutes such as DTPA into the vascular compartment may involve mechanisms that are distinct from those underlying the exudation of plasma from the microvasculature into the bronchial interstitium and lumen. Thus, DTPA clearance cannot be used as an index of microvascular leakage in the airways. Measurement of proteins in bronchoalveolar lavage fluid is a feasible means of assessing plasma exudation into the airways.

Recovery from small volume (20–30 ml) lavage may represent fluid sampled from the large airways and assays of specific proteins can provide an indication of the selectivity of the increase in plasma exudation. Thus, FICK *et al.* [9] reported that immediately after the local instillation of allergen, the concentrations of small molecular weight proteins in lavage fluid (*e.g.* albumin, transferrin and caeruloplasmin) increase, but the proteins with molecular weights greater than 345,000 daltons (*e.g.* alpha$_2$ globulin and fibrinogen) rise to a lesser extent. An increase in the recovery of labelled albumin in lavage fluid was reported by the same group following allergen challenge in man. Such studies are unfortunately limited in their application because of their invasive nature. The measurement of plasma exudation into the nasal passages has recently been attempted through the quantification of albumin levels in nasal lavage and may provide a model for the evaluation of the mechanisms controlling permeability changes in the distal airways.

Mechanisms

Many of the mediators implicated in asthma are capable of increasing airway microvascular leakage [7]. Ultrastructural studies of systemic microvascular beds support the view that the inflammatory leakage of protein-rich plasma does not occur in capillaries, but *via* widened gaps between the endothelial cells of postcapillary venules [47, 48]. Various inflammatory mediators are known to cause venular endothelial cells to contract actively, thus causing cellular separation, followed by movement of plasma proteins through the endothelial gaps, across the basement membranes of the endothelium and epithelium, with subsequent leakage into the airway lumen.

Blood flow

Protein extravasation is partially dependent on blood flow, although mediators such as PAF, which induces arteriolar constriction, are also extremely potent in increasing airway microvascular leakage [11, 12]. Furthermore, synergism between mediators which principally increase blood flow, such as PGE_2, vasoactive intestinal

peptide (VIP), calcitonin gene-related peptide (CGRP), and those which induce protein extravasation, such as the leukotrienes and bradykinin, has been demonstrated in the skin [49, 50].

Such interaction may not be relevant in the airways; thus, CGRP which is a potent vasodilator does not potentiate the airway response to substance P, which increases vascular permeability in guinea-pigs [51]. However, decreasing blood flow by alpha-adrenoceptor mediated vasconstriction does inhibit PAF-induced airway microvascular leakage whilst beta$_2$-adrenoceptor agonists such as salbutamol, which are vasodilators, have no enhancing effect [52]. One explanation for the lack of potentiation may be due to the relatively greater blood flow in airways compared to skin: potentiation is not possible where flow is adequate and may only be demonstrable where flow is reduced.

Mediators of inflammation

Most studies concerning the effects of inflammatory mediators on airway microvascular leakage have reported results following their intravenous administration to experimental animals. This systemic approach may influence the bronchial microcirculation by changing the perfusion pressure or *via* central reflex mechanisms. Few investigators have examined the effects of mediators administered by aerosol, or injected directly into the bronchial arteries. In asthma, mediators may be released locally within the airway lumen or interstitium, such that high local concentrations can be achieved without spill-over into the systemic circulation. Thus, the relevance of studying the effects of intravenously administered mediators may be questioned.

Histamine. In animals, intravenous histamine increased the permeability of bronchial venules of both submucosal and peribronchial plexuses to colloidal carbon *via* the transient formation of large endothelial animals [53, 54]. In the respiratory tract of the guinea-pig histamine is most active in the proximal large airways [55], with a prolonged effect lasting up to 30 min. Local instillation of histamine on to human nasal mucosa leads to increased recovery of albumin in nasal lavage fluid, suggesting transient increases in both epithelial and endothelial permeabilities [56].

Platelet-activating factor. PAF is one of the most potent inducers of microvascular leakage throughout the guinea-pig respiratory tract when administered intravenously [11, 12], being approximately 10,000 fold more potent than histamine, although its duration of action is shorter. The effect of *i.v.* PAF is not mediated *via* the secondary release of histamine, prostaglandins or sulphidopeptide leukotrienes, but is inhibited by the PAF receptor antagonists BN 52063 and WEB 2086 [12, 57]. PAF directly causes the contraction of human endothelial cells in culture [58], which permits the opening of endothelial gap junctions. Local perfusion of PAF in guinea-pig airways induces an increase in airway secretions suggesting extravasation of albumin from the vascular compartment through the endothelial and epithelial barriers [25]. In addition, intratracheal PAF induces the delayed leakage of plasma proteins into the airway lumen of guinea-pigs [59]. The antagonist BN 52021 also inhibits endotoxin-induced airway microvascular leakage in guinea-pigs, indicating a role for PAF [60]. It has been suggested that oedema resulting from increased airway permeability may be responsible for airway narrowing in human subjects after the inhalation of PAF, as PAF does not contract human airway smooth muscle *in vitro* [61, 62].

Leukotrienes. The sulphidopeptide leukotriene D_4 (LTD_4) is slightly less potent than PAF in increasing microvascular permeability in the guinea-pig when administered intravenously, although both are active throughout the respiratory tract [11, 55]. Leukotriene D_4 directly increases gap formation at the post-capillary venular endothelium as assessed by electron microscopy [63]. LTC_4 and LTD_4 both produce wheal and flare responses in human skin at low concentrations in a similar manner to PAF, although their effects on human airway vascular permeability are not known [64, 65].

Bradykinin. Intravenous bradykinin induces airway microvascular leakage [66], an effect that may be partly mediated through PAF release, possibly from the vascular endothelial cell [67] and partly *via* the release of prostaglandins [68]. Instillation of bradykinin to human nasal mucosa results in an increase in albumin and TAME-esterase activity, reflecting increases in vascular and epithelial permeability [69]. The observation that tissue kallikrein is present in the airways of stable asthmatic subjects [27] suggests that local generation of bradykinin may be responsible for airway oedema in asthma [27].

IgE-mediated responses. During IgE-induced anaphylaxis using intravenous antigen in sensitized guinea-pigs, plasma extravasation is mediated partly by histamine or leukotrienes, depending upon airway level [70]. Histamine release also contributes to leakage predominantly in the central intrapulmonary airways, but PAF does not appear to be involved in this response [57, 70]. These results are consistent with the preferential site of effect of these mediators in increasing microvascular permeability when applied exogenously [55]. Possible interactions between mediators released during IgE-mediated anaphylaxis remain to be examined and may be significant in asthma. Local instillation of antigen onto the respiratory mucosa of allergic asthmatic patients causes an increase in the total protein concentration of lung lavage fluid. In addition, an immediate increase in labelled serum albumin from the circulation into lavage fluid is observed [9]. Similar results have been obtained following the instillation of allergen onto the nasal mucosa of allergic subjects [71].

Neutrophil-mediated microvascular leakage

Neutrophils may play a significant role in the increase in microvascular permeability induced by several inflammatory stimuli such as LTB_4 [72, 73], complement fragments including C5a [74], and synthetic chemotactic peptides, for example F-met-leu-phe [72–74]. During the period of neutrophil migration, increases in skin vascular permeability to C52-des-arg are observed [73, 74]. Visualization of LTB_4-induced microvascular leakage in the hamster cheek-pouch has shown that it occurs at sites of neutrophil adherence in post-capillary venules. However, more recent work suggests that neutrophil adherence and diapedesis in response to LTB_4 in this model occur without protein leakage [75]. These studies have not been performed in the airways and it is possible that the passage of inflammatory cells through the epithelium into the airway lumen does not influence epithelial permeability to plasma proteins.

The attachment of neutrophils to endothelial cells involves changes on both the endothelial and leucocyte surfaces and there is evidence to suggest that a three-protein membrane complex on the leucocyte, the CDw18 glycoprotein complex, is required for neutrophil attachment [76]. On the endothelial cell surface a number of factors, such as bacterial lipopolysaccharides and interleukin 1, cause increased adhesiveness to leucocytes [77]. The exact nature of the interaction between venular endothelial cells and circulating neutrophils, however, remains to be established. Neutrophils adhere and traverse vascular endothelium in the presence of several chemotactic stimuli [78]. Ultrastructural studies have shown that migration occurs *via* intercellular junctions without apparent injury to endothelial cells [79, 80]. However, under certain conditions, neutrophils do damage endothelial cell junctions *via* the action of protease enzymes and reactive oxygen species [81].

Increased vascular permeability cannot be induced by C5a in rabbits depleted of circulating neutrophils, although responses to histamine and bradykinin are unchanged [73]. In guinea-pigs, the increase in tracheal vascular permeability induced by toluene di-isocynate (TDI) requires the presence of neutrophils [82]. Bacterial endotoxin increases vascular permeability of the pulmonary circulation to Evans blue dye, an effect dependent on the presence of neutrophils [83]; it also increases bronchial vascular permeability with a slow onset of action, which may reflect the time required for leucocyte recruitment [60].

Neural mechanisms in microvascular leakage

Nerve stimulation. Electrical stimulation of the distal end of the sectioned cervical vagus nerve evokes an increase in bronchial vascular permeability in the trachea and main bronchi of the rat [32] and guinea-pig [84]. Efferent vagal motor nerves do not seem to be involved because the effect is not blocked by either ganglionic blockade or antagonism of muscarinic receptors [32]. Capsaicin, which depletes sensory nerves of neuropeptides such as substance P (SP) [85], inhibits the vagally-induced increase in microvascular leakage suggesting that release of sensory neuropeptides is involved in neurogenic plasma extravasation [32]. Furthermore, SP antagonist drugs partially inhibit vagally-induced increases in airway oedema [84]. The increased airway vascular permeability attributable to histamine, bradykinin and acutely-administered capsaicin is inhibited by capsaicin pretreatment, suggesting that sensory nerves are involved in mediating these responses [86]. Inflammatory stimuli, such as cigarette smoke, induce plasma leakage into the airways, an effect which has been shown to be mediated by capsaicin-sensitive vagal afferents [87]. However, capsaicin pretreatment does not inhibit TDI-induced tracheal plasma extravasation [88], which seems to be neutrophil-dependent [82].

Neuropeptides. In addition to SP, two other structurally-related peptides (tachykinins), neurokinin (NK) A and B, have recently been identified and neurokinin-like immunoreactivity has been observed in the lung. SP, NKA and NKB induce plasma exudation [51] and are all possible mediators of neurally-induced microvascular leakage. Whether they act directly on venules or stimulate the production of other mediators, which in turn increase vascular permeability, is not known. SP-induced plasma exudation is not mediated by neutrophils [89], although SP may cause adherence of leucocytes to venular walls [90]. It is possible that the dense SP-immunoreactive nerves in the airway epithelium release neuropeptides, which then diffuse to affect venular endothelium, since there are few nerves localized near venules [91].

Sensory nerve stimulation may cause other cells within the airway epithelium to release other mediators known to increase plasma exudation, including leukotrienes C_4 and D_4 [92]. In the rat, vagal nerve stimulation causes goblet cell discharge as well as increasing epithelial permeability [91]. Opioid peptides prevent plasma exudation, during vagal nerve stimulation in the guinea-pig by a pre-synaptic mechanism involving inhibition of release of neuropeptides from sensory nerve endings in the airways [93]. Clearly, such neural control mechanisms have been carried out mainly in rodents. Information concerning higher species or man is unavailable, although preliminary data suggest that local application of substance P and capsaicin to the human nasal mucosa does not result in plasma exudation [94]. Whether the distal airways will behave similarly remains speculative.

Therapeutic aspects of airway microvascular leakage

Despite the importance of airway plasma exudation in asthma, relatively little is known about the influence of currently available anti-asthma drugs on this process.

Adrenergic drugs

Beta-adrenergic agonists have been shown either to have no therapeutic action or to exhibit inhibitory effects

on plasma leakage in several microvascular beds [95, 96], despite the fact that they cause vasodilatation which, in skin, potentiates microvascular leakage [74]. This suggests that beta-agonists may have a direct effect in preventing venular endothelial contraction. Terbutaline, for example, attenuates histamine and leukotriene-induced microvascular leakage in the trachea of cats and guinea-pigs [97, 98].

In a superfused tracheal preparation of the intact guinea-pig, small doses of intratracheally administered terbutaline inhibit capsaicin-induced leakage of FITC-dextran into the trachea and main bronchi, although terbutaline has no effect on neurally-induced tracheal microvascular leakage of Evans blue dye in the rat [99]. Similarly, salbutamol does not influence PAF-induced microvascular leakage in guinea-pig airways [52]. The reasons underlying these conflicting observations are not clear although the different results indicate that tissue oedema and plasma leakage into the airway lumen may not necessarily be linked. Nevertheless, adrenaline is highly effective in preventing leakage, perhaps by limiting blood flow to the sites of leakage *via* its vasoconstrictor properties [52]. The effects of adrenaline are probably mediated *via* alpha-receptors localized to precapillary arterioles.

Methylxanthines

Methylxanthines inhibit histamine-induced microvascular leakage in hamster cheek pouch [100], and capsaicin-induced leakage in guinea-pig airways [59] but do not inhibit PAF-induced microvascular leakage in the airways of guinea-pigs [52]. However, it remains an intriguing possibility that the partial protection afforded by theophylline and enprofylline against the late phase response to antigen [101] may be *via* alterations in airway oedema formation. Theophylline also inhibits the delayed leakage of plasma proteins into the airways induced by intratracheally-administered PAF in the guinea-pig [59].

Corticosteroids

High doses of glucocorticosteroids prevent the increase in microvascular permeability induced by histamine and bradykinin *via* mechanisms that are independent of changes in blood flow, microvascular pressure, perfused surface area or specific mediator receptor blockade [102]. Dexamethasone inhibits plasma leakage induced by both PAF and antigen in rat airways [103].

Mediator antagonists

Since many different mediators with the potential to increase airway microvascular leakage may be released during the asthmatic inflammatory process [7], it is unlikely that a single antagonist will prove useful. Despite the potent effect of PAF in increasing microvascular permeability, PAF antagonists do not inhibit ovalbumin-induced leakage in sensitized guinea-pigs [57, 71] although FPL 55712, a leukotriene antagonist, has a partial inhibitory effect [70].

Other drugs

Calcium antagonists such as verapamil inhibit microvascular leakage in the hamster cheek pouch possibly by preventing contraction of the intracellular contractile elements responsible for gap-formation between endothelial cells [104]. In guinea-pig airways, verapamil has an inhibitory effect on leakage at certain doses although higher and lower doses are without effect [52]. Potassium channel activators are currently under investigation as therapy for a number of diseases in humans [105]. However, their vasodilatory effects are likely to preclude them from use in inhibition of microvascular leakage and we have found that the potassium channel-blocker cromakalim had no inbitory effect on PAF-induced leakage in guinea-pig airways (Rogers and Boschetto, unpublished observations).

Conclusion

Plasma exudation into the airways appears to play a significant role in the pathogenesis of asthma. However, further work is needed to evaluate its precise contribution, but is impeded by lack of satisfactory, non-invasive methods for measurement of plasma exudation in the airways. Because airway oedema is likely to be an important feature in asthma, future research should be aimed at developing anti-asthma drugs which specifically prevent airway microvascular leakage.

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Le rôle de l'augmentation de perméabilité micro-vasculaire des voies aériennes et de l'exsudation plasmatiques dans l'asthme. K.F. Chung, D.F. Rogers, P.J. Barnes, T.W. Evans.
RÉSUMÉ: L'oedème des voies aériennes et l'inflammation sont considérés comme des caractéristiques essentielles de l'asthme; elles résultent d'une perméabilité micro-vasculaire accrue dans la circulation bronchique, avec exsudation de plasma et de cellules inflammatoires das la lumière des voies aériennes. La résistance aux courants aériens est accrue et l'épithélium est lésé, soit directement, soit par les protéines cytotoxiques provenant des cellules inflammatoires migratrices. Les médiateurs en cause sont la bradykinine, le PAF, les leukotriènes et l'histamine. L'inflammation induite par les antigènes et l'inflammation neurogène produite par les IgE et les neuropeptides, respectivement, peuvent également contribuer à la production d'oedèmes. L'appréciation de l'augmentation de la perméabilité vasculaire bronchique chez les animaux a reposé largement sur la mesure de l'extravasation d'albumine radio-marquée ou de colorants liés aux protéines. Les techniques non invasives sont moins valables chez les hommes, mais la mesure du taux de clearance des particules inhalées, marquées par un isotope, peut être couronnée de succès. L'oedème des voies aériennes est une caractéristique importante de l'asthme, et les recherches futures devraient avoir pour objet le développement de médicaments qui préviennent spécifiquement la fuite micro-vasculaire au niveau des voies aériennes.
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