Plasma-derived proteins in airway defence, disease and repair of epithelial injury


ABSTRACT: One significant characteristic of the airway mucosa in vivo, that cannot easily be mimicked in vitro, is its microcirculation, which generates a highly dynamic, biologically active milieu of plasma-derived molecules that may pass to the airway lumen in vivo.

New data on the mechanisms of airway mucosal exudation indicate that the protein systems of circulating plasma may contribute significantly to the biology and immunology of the lamina propria, its surface epithelium and the luminal surface, not only in injured airways, but also in airways that are activated but display no sign of oedema, epithelial disruption, or increased absorption capacity.

We suggest that present knowledge of the mechanisms of plasma exudation, together with rapidly emerging information (not detailed herein) on receptors, target cells and cellular responses to the plasma-derived molecules, must be considered in any realistic model that investigates "immuno-inflammatory" mechanisms of the airway mucosa.


interplay between plasma-derived molecules, their receptors and airway epithelial cells and their secretions in vivo, which affect airway defence or induce disease.

**Extravasation of plasma from the mucosal microcirculation**

In human nasal and tracheobronchial airways and in guinea-pig trachea there is a profuse network of microvessels immediately beneath the pseudostratified epithelium (figs. 1, 3). When the airways are subjected to an inflammatory insult, the endothelium of the post-capillary venules of the bronchial microvasculature is promptly affected by agents that alter its permeability [3, 4, 6, 11]. Mediators such as bradykinin, histamine, leukotriene D4, platelet activating factor (PAF)-acether and others, applied topically to the airway mucosa, produce a marked increase in bronchial venular permeability [6, 11]. The formation of small interendothelial pores is associated with increased permeability [3, 12, 13] (fig. 3). Through these pores bulk plasma is driven into the extravascular space by hydrostatic pressure forces. Local colloid osmotic pressure gradients are thus abolished [14] and the lamina propria becomes endowed with macromolecules. Complete distribution of plasma into the extracellular matrix of the subepithelial zone may be accomplished during the first minute after mucosal challenge [7]. Virtually "nonsieved" plasma also traverses the epithelial basement membrane and moves up between surface epithelial cells, gaining entry into the airway lumen [1, 6, 7] (fig. 1).
The nonsieved nature of exuded plasma

The maintenance of plasma-like concentrations by different-sized proteins in the airway lumen indicates that molecules ranging from albumin (60 kDa) to \(\alpha_2\)-macroglobulin (700 kDa) may all move equally and swiftly across all the barriers that exist between the venular compartment and the luminal surface of the airway mucosa (fig. 4) [1, 6, 15]. As a corollary, the acute bronchial exudative response to allergen challenge may be best measured by the increase in bronchoalveolar lavage (BAL) fluid levels of large proteins such as \(\alpha_2\)-macroglobulin [16]. BAL albumin levels are already high and variable at baseline; albumin is, therefore, not always a reliable index of bronchial exudation of plasma [15].

Due to unknown degrees of concentration (or dilution) the actual volumes of the plasma exudate entering the airway lumen have not been assessed. A cautious estimate is that less than 1 mL of bulk plasma enters the nasal passages during an acute allergic reaction with symptoms. The limited volume that is exuded per unit time further underscores the notion that its content of bioactive proteins and peptides is probably of greater importance than whether or not oedema develops.

Bioactive molecules of the plasma exudate

In airway conditions where there is exudation, the lamina propria, the epithelial basement membrane, the epithelial lining and the mucosal lumenal surface are endowed with pluripotent protein systems that are normally, in less active forms, retained within the vascular compartment [15] (fig. 5). The extravasated plasma contains adhesive and leucocyte-activating proteins such as fibrin(ogen) and fibronectin [4, 19–21]. These plasma-derived proteins are laid down along pathways [7], which include the paracellular epithelial routes through which leucocytes pass to the lumen (fig. 1). The complement family and the coagulation cascade of bioactive molecules have been extensively examined [22, 23] and their potential roles in the airway mucosa deserve attention. For instance, fibrin degradation products act as potent growth factors on a variety of cells [24, 25].

Other examples of plasma-derived mediators include kinins, immunoglobulins, proteases and antiproteases. Plasma further contains cytokines that, despite their low concentrations, may well exert biological actions [26]. Through its capacity to target other molecules [27], \(\alpha_2\)-macroglobulin may have profound influences on cytokines and other
Fig. 3. – Light micrographs demonstrating subepithelial venules in airway mucosal wholemount preparations. The endothelial cell borders are outlined as silver-stained black lines. They are intact in baseline conditions (a, b). In airways challenged with inflammatory mediators the endothelial cells become distinctly separated producing small round holes or pores (arrows; c) through which bulk plasma exits. If the inflammatory response has the capacity to recruit leucocytes, these will also exit across the venular wall (arrows; d) but not through the pores. Data are from reference [3] and unpublished observations (see also references [12, 13]. Internal scale bars: a) 150 µm; b), c) and d) 20 µm.

<table>
<thead>
<tr>
<th>Condition</th>
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Fig. 4. – Acute human airway exudation of bulk plasma. a) histamine (400 µg·mL⁻¹) causes mucosal exudation of albumin (not shown) and α2-macroglobulin in human nasal airways. b) the mucosal exudation response involves little sieving of the plasma macromolecules, as indicated by similar concentration ratios between albumin (MW 69 kDa) and α2-macroglobulin (MW 700 kDa) in plasma and on the surface of the histamine-challenged airway. Note that histamine, even at 2,000 µg·mL⁻¹, may not affect the nasal mucosa as an absorption barrier [5]. Histamine inhalation and endobronchial allergen application also cause prompt bronchial mucosal exudation of α2-macroglobulin as determined in samples of c) induced sputum and d) bronchial lavage, respectively. Data are from references [16–18] and published observations. *, **: p<0.05, p<0.01 versus baseline. NAL: nasal airway lavage; BAL: bronchoalveolar lavage.
Fig. 5. — The exudation process will rapidly and efficiently distribute a variety of plasma-derived, bioactive molecules throughout the extracellular matrix in the subepithelial tissue, the epithelium, and airway lumen. Cell-derived proteins in the airways (see below). Taken together, an overwhelming variety of plasma-derived molecules, including as yet unidentified proteins and peptides, will participate in the process of airway inflammation which normally serves to protect the host by a transient defence reaction [2] or, if inappropriate and chronic, may be injurious [3, 15].

Epithelial passage of bulk plasma

Extravasated bulk plasma readily traverses a normal airway epithelial lining [1]. Accordingly, the acute extravasation response may not lead to mucosal oedema [6] or to increases in airway lymph node levels of plasma proteins; the exudation process may, thus, occur and yet not be detectable by the commonly used analytical methods [6, 28, 29].

Contrary to current beliefs, luminal entry of bulk plasma causes no disturbances of the pseudostratified epithelial lining, which remains uncompromised, both structurally (as assessed by light microscopy and transmission electron microscopy), and functionally (determined by absorption of small and large molecules) [2, 5]. In an as yet unexplained manner, the extravasated macromolecules pass through the epithelial tight junctions situated at the apicodental borders of the epithelial cells. It is these specialized membrane structures that are the final selectively permeable barrier to the passage of the plasma into the airway lumen [30] (fig. 6). As with the alveolar lining epithelium, it is the “tightness” of the epithelial tight junctions that largely determines whether tissue oedema will follow bulk extravasation of plasma. Whilst the occurrence of luminal entry of bulk plasma, without impeding the capacity of the mucosa to act as an absorption barrier, is a potent first line respiratory defence response [2], questions remain with regard to the mechanisms involved. How could the airway epithelium, famous for its tightness, suddenly let through molecules the size of α2-macroglobulin?

One of the few possibilities compatible with the many observations on luminal entry of bulk plasma in both animals and humans was that the extravasated plasma itself had caused its own epithelial passage, by mechanisms involving an increased basolateral pressure load on the epithelial surface cells [32]. This hypothesis (fig. 5) was testable. It required a system in which the epithelial barrier could be examined separately from that of the microcirculation; otherwise the mucosa should remain as it is in vivo. Such a test system was achieved in the carefully isolated tracheal tube preparations, maintained in an organ bath and mounted such that serosal and mucosal surface solutions were separated, allowing studies of the influence of a hydrostatic pressure load on either side of the epithelium. Extreme care was required to avoid edge trauma yet still provide control over hydrostatic pressure changes and sampling procedures [32].

Observations made in the intact tube preparation [5, 32] support the above hypothesis by demonstrating that: 1) the extravasating bulk plasma moving between the columnar epithelial cells needs to increase the local hydrostatic pressure by only a few cmH2O to create ubiquitous paracellular passage routes for macromolecules into the lumen (paracellular stretches of 30–40 m would be available for this passage per square centimetre of mucosal surface); 2) the luminal entry operates without the need for the pharmacological effects of mediators that act directly on the epithelial barrier [32]; and 3) the hydraulic ("plasma exudate-epithelial") mechanism of luminal entry of macromolecules exhibits reversibility, repeatability and direction-selectivity in agreement with the in vivo observations [5].

Neurogenic exudative inflammation - burnt out?

Using a compressible nasal "pool device", a well-defined area of airway mucosal surface can be kept in contact with known concentrations of agents and tracers. After the decided length of exposure time the instilled fluid is readily recovered into the "pool device" providing the opportunity to quantify exclusively from the area of interest [33]. As a lavage procedure the nasal pool method can be repeated ad libitum apparently without causing disturbances to the nasal mucosa. Exudative responses can, thus, be examined to advantage in the nose. Furthermore, the findings in the nose may also reflect those that occur in the human tracheobronchial tree [17]. The contractile and secretogogue effects of the neurotransmitter acetylcholine, and its analogues (e.g., methacholine, carbachol) are virtually without exudative effects in nasal and bronchial airways of animals and humans [6, 34]. In human nose, irritants such as nicotine and capsaicin, evoke pain and mucin secretion (assessed as luminal fucose), but no plasma exudation [35, 36] (fig. 7). Thus, at maximal secretory doses [35] in healthy subjects as well as in patients suffering from allergic rhinitis we could not detect a trace of neurogenic exudation [35, 36] (unpublished observations). Admittedly, these observations cannot disprove the possibility that large doses of capsaicin may still be associated with leakage of plasma, as has been reported recently [32]. The negative nasal findings have recently been extended to human bronchi, in which inhalation of histamine was found to increase the luminal entry of α2-macroglobulin by several times, whereas significant...
cough-inducing capsaicin inhalations were completely lacking in this effect [37] (measured as concentrations of \(\alpha_2\)-macroglobulin in induced sputum). Such human data (fig. 7) are in contrast to findings in the airways of healthy guinea-pigs: here agents such as capsaicin produce pronounced exudation of bulk plasma into the airway lumen [39, 40]. Whilst rodent data are now the basis for a widely acknowledged notion of "neurogenic airways inflammation", we suggest that the phenomenon of neurogenic airway inflammation is more relevant to rodents than to humans.

**Exudative agents**

In contrast to neuropeptides, leukotriene-type mediators (histamine, bradykinin, leukotriene D\(_4\), PAF-acether \(\textit{etc} \)) produce graded exudative responses over a wide range of concentrations in both guinea-pig and human airways [6, 11, 33, 39–42] (cf. figs. 4 and 7). There is also the possibility that exudative agents act through inhibition of mucosal nitric oxide that may tonically suppress airways plasma exudation [43]. Eosinophil granule proteins increase vascular permeability in the hamster cheek pouch [44], and in guinea-pig trachea (unpublished observations by Erjefält \textit{et al.}). Certain cytokines, proteases and fibrinolytic peptides may also induce a prompt exudative response as will any agent that has a capacity to release vasoactive agents \textit{in vivo}. A variety of autacoids cause extravasation of plasma in the systemic microvascular beds of many organs, including the airways [45, 46]. It should be noted that the pulmonary microvasculature, in

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**Fig. 6.**  – a) after extravasation, bulk plasma moves up between epithelial cells in the challenge area. Through a slight hydrostatic pressure load (<5 cmH\(_2\)O) on the basolateral aspects of the epithelial cells, potentially caused by the extravasated plasma itself. b) unidirectional flux of macromolecules into the airway lumen is effected. c) thus, bulk plasma appears on the mucosal surface without loss of epithelial integrity. The hypothesis is that the intact airway epithelial lining has a hydraulically operated valve function, in agreement with a wide range of \textit{in vivo} data and directly supported by findings in intact airway tube preparations (see text). d) a light micrograph illustrates extravasated gold particles between and around epithelial cells a few minutes after local allergen challenge of the airway mucosa of sensitized guinea-pigs. The exceedingly small extracellular space in the tight junctional area makes it almost impossible to observe the passage of plasma tracers in this apical paracellular region. e) example of a tight junctional belt as seen by freeze fracture-transmission electron microscopy found in the ciliated epithelium of a human main bronchus. The belt is comprised of many interconnecting strands/grooves (arrows) indicating by the "count strand hypothesis" of Claude [31] that the barrier formed by the junction is relatively "tight". (Data from references [7, 30] and unpublished observations). C: cilia. Internal scale bars: d) 6 \(\mu\)m; e) 0.5 \(\mu\)m.
contrast to that of the bronchial (systemic) microcirculation, is insensitive to several common inflammatory mediators such as histamine [14, 46].

Nasal and endobronchial challenge experiments have demonstrated that the human airway mucosa responds to allergen with prompt luminal entry of bulk plasma, which includes α₂-macroglobulin and fibrinogen [16, 18, 21]. Allergen challenge in subjects with allergic asthma produces both immediate and late-phase responses during which there is plasma exudation [16, 47]. In guinea-pigs, challenge of the tracheal mucosa by allergen (in sensitized animals) or PAF-acether also produces similar dual plasma exudation responses [40, 48, 49]. The immediate phase is largely over within 1 h. It is followed by a “late phase” of airway exudation that peaks about 5 h after challenge. Single dose topical treatment with clinically effective anti-asthma steroids prevents the late phase exudation [10, 50].

In contrast to allergens, the small molecular weight occupational chemical, toluene-diisocyanate (TDI), evokes plasma exudation responses in airways that have not previously been exposed to TDI. Within the dose range of 20–200 pmol, TDI produces dose-dependent plasma exudation into guinea-pig airways [6, 8]. These doses, applied to a defined surface area of the large airway of guinea-pigs, may be compared to the accepted occupational exposure level which corresponds to a daily human body burden of about 100 pmol TDI. Following a single dose of TDI, exudation starts promptly, peaks 5 h after challenge, and continues for about 15 additional hours (fig. 2). Longstanding epithelial and smooth muscle abnormalities ensue; tracheobronchial tone and the number of secretory cells are significantly increased several weeks after the single TDI challenge [8].

Guinea-pigs that receive repeated challenges with 20 pmol of TDI given to large tracheobronchial airways develop an increased inflammatory responsiveness to TDI [9]. Thus, challenge with exceedingly low doses of TDI (2 pmol), in sensitized animals, is associated with a marked and sustained exudative response and a pronounced eosinophilia (fig. 2). This TDI-induced exudative response, in contrast to that observed in nonsensitized animals, is inhibited by glucocorticoid pretreatment [9]. The mediators involved in plasma exudation evoked by such low and occupationally relevant doses of TDI have not yet been determined.

Fig. 7. – Inflammatory mediators such as: a) histamine; b) bradykinin; and c) leukotriene D₄ (LTD₄) are effective exudative agents in human nasal airways, as is d) allergen in allergic individuals. However, at doses which produce pain and mucus secretion, neurogenic agents such as: e) nicotine ( albumin; fucose) and f) capsicain ( prior to season; late in season) have not induced plasma exudation in the human nose. g) inhalation of capsicain causes strong cough responses but bronchial mucosal exudation of plasma is not detected. (Compare with figure 4, where histamine inhalation-induced exudation is given as a positive control). Data are from references [16, 17, 33, 35–37] and unpublished observations. *, **, ***: p<0.05, p<0.01, p<0.001. NAL: nasal airway lavage; BAL: bronchoalveolar lavage.
"Induced exudation" to monitor airway inflammation

Many molecules are bound by albumin and, for example, α2-macroglobulin has a demonstrated capacity to bind cytokines [27] and eosinophil cationic protein (ECP) [51]. Hence, it is anticipated that the exudative process may bring with it significant numbers of markers of inflammation (i.e., pro-inflammatory mediators present in the extracellular compartment of the inflamed mucosa), to the airway surface [15]. New observations may already support this hypothesis. Acute exudations of α2-macroglobulin, induced by nasal histamine challenges in subjects with allergic rhinitis, have been associated with significantly increased luminal levels of IL-6 [52]. Woolley et al. [53], examining effects of allergen challenge in allergic asthma, have recently observed increased luminal levels of granulocyte-monocyte colony stimulating factor (GM-CSF) in the bronchi along with decreased mucosal tissue levels of this cytokine. We speculate that these data may, in part, be explained by their transport during plasma exudation, which is probably evoked by the allergen challenge [16], bringing tissue cytokines to the airway lumen [15].

Both in the nose and the bronchi, histamine challenge-induced exudation has been instrumental in the demonstration of elevated eosinophil cationic protein (ECP), otherwise not evident in lavage and sputum samples. The "induced exudation" method has, thus, uncovered eosinophilic activity in the nasal mucosa of allergic asthma [54]. Equally, the "induced exudation" disclosed a significant bronchial eosinophilic activity (i.e., increased sputum ECP levels) in adult subjects suffering from seasonal allergic rhinitis [55].

One basic functional aspect of our hypothesis is that the process of exudation normally serves to rid the airway mucosa of potentially harmful molecules [2, 15]. Another inference is that plasma exudation may be an important determinant of bioactive molecules of the airway mucosa in vivo, not only in its own right, but also with regard to local distribution of cell-derived molecules. Finally, one of the practical corollaries is that the dual induction method, "induced exudation" followed by induced sputum, may prove to be a valuable procedure in the future, which could provide an insight into the nature of bronchial inflammation in distinct airway diseases and conditions [55].

Epithelial shedding-induced plasma exudation

Epithelial shedding to the point of denudation, may induce several tissue responses that may primarily serve to heal damaged areas. Potentially the most important repair and defence-promoting response organ during the first phases of repair is the mucosal microcirculation. Within a minute after epithelial shedding in vivo, interendothelial permeability-pores are formed along the venular wall (fig. 3) and a pronounced, local exudative responses is initiated [3, 4]. Extravasated bulk plasma immediately enters the airway lumen at the site of denudation where a gel-like network of fibrin and fibronectin fibres, with other included plasma proteins, is formed on the denuded but intact basement membrane [4, 58]. Thus, the local extracellular milieu will be endowed promptly with plasma-derived molecules such as fibronectin (fig. 8) having defence, and repair-promoting activities [20]. Another tissue response, which is initiated by epithelial shedding, is the local recruitment and activation of leucocytes (fig. 3) including the activation of eosinophils in the airway wall [3, 58]. During the first few hours after epithelial shedding in vivo there is increased exudation of plasma that continues until a new epithelial cell cover is present. Then, there is increased proliferation both in the epithelium and in subepithelial fibroblasts and smooth muscle cells at the site of the lesion [58].

There is a wealth of data (and concepts) arising from experimental systems in vitro: cell culture studies totally dominate the current epithelial research scene. This may be unfortunate, as the in vivo events in this field of investigation (epithelial injury-restitution processes and their sequelae) may not readily be mimicked experimentally in vitro where epithelial cells dwell in culture media. These are some of the recently unravelled features of epithelial restitution following epithelial shedding as they occur in the relevant in vivo milieu [58, 63]. Allergen challenge-induced epithelial patches of injury are dynamic foci where concomitant epithelial shedding and repair processes occur in an exudate-derived molecular milieu [59, 60] (fig. 8). Eosinophil cytolysis and large numbers of clusters of free eosinophil granules (Cfegs) are also associated with these sites [59, 64]. The patchy accumulation of activated leucocytes and potent plasma-derived proteins agrees with findings of conglomerates of shed epithelia, necrotic leucocytes, Cfegs and plasma proteins in airway discharge material in asthma and allergic rhinitis [65–68]. Another clinical inference is that the early appearance of a continuous lining following epithelial restitution after injury may in part explain the findings of an unchanged, or even a decreased, airway absorption permeability in allergic airway disease [3, 69]. The pluripotential roles of events associated with epithelial shedding-restitution in the pathogenesis of airway diseases have been reviewed elsewhere [61, 62].

Role of plasma exudation in disease

Even if extravasation of plasma into the airway tissue frequently does not produce mucosal oedema, there are several other sequelae to be considered [65, 70]. As discussed above, plasma is an important source furnishing the mucosal extracellular matrix with protein components having multiple biological activities, without which airway inflammation may not develop. Because of its physical properties and interactions, a plasma exudate may impede the patency of the lower airway passages in several ways, which have been described [65, 70]. Exuded plasma may accumulate in the airways, particularly during late night and early morning hours [17]. It contributes to so-called "mucous plugs" that are actually "plasma-mucous plugs" [71]. Against a background of mucosal thickening and stagnated exudate mucous in the lumen, an attack of asthma may create severe and life-threatening obstruction of the bronchi, even with moderate bronchial smooth muscle contraction [70]. Schiønning et al. [56], who examined plasma proteins in sputum samples, concluded that plasma leakage in asthma correlates with airway responsiveness.
Fig. 8. — Epithelial injury-repair in guinea-pig allergic airways 1 h after allergen exposure. The regular mosaic pattern of epithelial cells is interrupted by patches of epithelial injury-repair processes. This is shown by light microscopy (aerial view) in: a) wholomount preparation where apical epithelial cell borders have been silver-stained, and b) by scanning electron microscopy. c) Schematic depiction of the epithelial injury-repair process and its sequelae. Damage may proceed apically while rapid repair covers the basement membrane with restitutional cells. The injury-repair sites are intense and dynamic foci of inflammatory processes. The molecular milieu may be dominated by plasma-derived proteins and peptides. Activated neutrophils and eosinophils occur here together with epithelial cell debris in a fibrin-fibronectin gel. The sequelae to simple epithelial shedding in vivo further include remodelling effects involving not only the epithelium, but also fibroblasts, smooth muscle cells and regional lymph nodes. (Data and concepts are from references [3, 4, 57–62].)
Beside the pathogenic potential of the exuded molecules, these may also serve in defence, repair and the prevention of infection. For example, bulk plasma exudation occurring at the height of corona virus-induced common cold [72] may contribute to the acute inflammation, but can also favour a rapid resolution of this condition. The role of exuded plasma may be exaggerated in inflammatory airway diseases, because in these conditions the endothelium may be particularly sensitive to mediators that increase the venular permeability. This exudative hypertresponsiveness has been demonstrated as an abnormally large exudative response to histamine challenges in allergic and infectious rhinitis [73, 74]. However, exudative hypertresponsiveness is not a consistent feature of inflammatory airway diseases [42].

**Antiexudative effects of drugs**

The venular endothelial cell is a target both for exudative agents and for molecules that produce antiexudative effects by direct vascular antipermeability mechanisms [14, 42]. Antihistamines, therefore, have a predictive antiexudative efficacy in airways where a significant histamine-induced tone exists. Similarly, leukotriene-inhibitory drugs would be effective antiexudative agents under conditions when leukotrienes contribute significantly to airway exudation. β2-agonists, chromones and theophyllines reduce inflammatory challenge-induced plasma exudation responses in guinea-pig airways [11, 28]. This action may reflect direct functional antagonism of the venular wall since the effect appears not to depend upon which mediator is used to evoke the exudation. Furthermore, these antiasthma drugs may not reduce airway mucosal blood flow [28].

The long duration of action of topical formoterol given to animal airways was first observed in respect of its potent anti-exudative effect [75] (fig. 9). In subjects with seasonal allergic rhinitis, topical nasal applications of high doses of terbutaline reduced allergen challenge-induced levels of plasma proteins (α1-macroglobulin) and mast cell mediators (tryptase) in fluid lavaged from the mucosa [18]. However, due to lack of human data it is not known whether any drug other than steroids exerts clinically significant antiexudative effects in the airways. Antiexudative drug effects (fig. 9) that reduce the functional reactivity of the mucosa to inflammatory stimuli, may be desirable in the treatment of asthma and other inflammatory airway conditions. However, the exudative response, required for respiratory defence and repair, should not be impeded during such treatment.

The antiexudative efficacy of systemic steroid treatment was reported when the plasma proteins began to be detemined in airway discharges in asthma and rhinitis. Notably, the steroid-induced inhibition of exudation occurred without concomitant reduction in indices of secretion pre-sent in sputum [76]. A poor antiserotonic effect of steroids supports the notion that plasma exudation closely reflects airway inflammation [17, 77]. As reviewed elsewhere [77] airways exudate not only differs from epithelium-derived secretions through its content, but the processes behind these two mucosal outputs also have a qualitatively distinct pharmacology and physiology regarding both their induction and inhibition.

**Anti-inflammatory drugs**

Increased levels of vasoactive agents

**Pharmacological antagonists**

**Functional antagonists**

**Inflammatory processes**

Fig. 9. – Different mechanisms by which drugs may reduce airways plasma exudation. Anti-inflammatory drugs, such as steroids, inhibit inflammatory processes and may, thus, indirectly prevent the increased microvascular permeability. Pharmacological antagonists, such as anti-histamines, inhibit the venular permeability effect of a single mediator. Functional antagonists, such as β2-agonists, act on the venular endothelium making it generally less responsive to the vasoactive agents.

**Conclusion**

Current studies of immuno-inflammatory mechanisms of airway mucosa largely concern the functions and biochemistry of cultured cells dwelling in defined, but artificial, ex vivo solutions. Unfortunately, the in vitro data do not always translate well in to the dynamic situation in vivo [84]. Important aspects of airway inflammation, defence and repair (and airway drugs) may, thus, have to be unravelled directly in the complex, but relevant, biosystems that include an active microcirculation; i.e., in human airways in vivo [17] and animals models [85]. Recent examples of discoveries in vivo, that have not been predicted by in vitro research paradigms, include activation of airway mucosal eosinophils, through a regulated cytolytic
mechanism [64], and the processes of airway epithelial shedding and restitution which may be associated with disease [61, 62]. It is of note that these eosinophilic and epithelial events occur in close association with airways exudation.

An active microcirculation generates a highly dynamic, biologically active milieu of plasma-derived molecules. New data on the mechanisms of airway exudation suggest that the protein systems of circulating plasma may contribute significantly to the biology and immunology of the airway mucosal tissue, yet the mucosal surface, not only in injured airways, but also in activated airways, may display no sign of oedema, no sign of epithelial disruption and no sign of increased absorption capacity. The extent or lack of tissue oedema may depend critically on the plasticity of the epithelial tight junctions, which readily allow the movement of plasma to the airway lumen. The present considerations together with the rapidly growing quantity of information (not detailed herein) on receptors, target cells and cellular actions of the plasma-derived molecules and the interactions of plasma with the epithelium-derived secretions, which have formed the focus of the present series, may have to be considered in realistic models of "immuno-inflammatory" mechanisms of the airway mucosa.

Appendix: definitions

Airway exudation comprises: 1) extravasation of bulk plasma from postcapillary venules belonging to the airway mucosal microcirculation that carries systemic blood; and 2) the further movement of nonsieved plasma exudate into the extracellular matrix of the lamina propria, across the basement membrane, between epithelial cells, and into the airway lumen.

In contrast to the "transudation" of protein-poor fluid the mucosal exudate is typically nonsieved and contains all the large plasma proteins.

Airway exudation does not encompass cell traffic that is regulated by separate mechanisms. Although luminal entry of bulk plasma occurs without comprising integrity and the normal barrier function of the epithelial lining, airway exudation is entirely distinct from airway secretory processes.

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References


11. Persson CGA, Erjefält I, Andersson P. Leakage of macromolecules from the vascular compartment into the airway lumen, yet the mucosal surface, not only in injured airways, but also in activated airways, may display no sign of oedema, no sign of epithelial disruption and no sign of increased absorption capacity. The extent or lack of tissue oedema may depend critically on the plasticity of the epithelial tight junctions, which readily allow the movement of plasma to the airway lumen. The present considerations together with the rapidly growing quantity of information (not detailed herein) on receptors, target cells and cellular actions of the plasma-derived molecules and the interactions of plasma with the epithelium-derived secretions, which have formed the focus of the present series, may have to be considered in realistic models of "immuno-inflammatory" mechanisms of the airway mucosa.

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