THE WRECKING OF THE WRAPPING: THE AIRWAY EPITHELIUM, A PRIME TARGET FOR INHALED ORGANIC DUSTS

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Abstract

Several mediators that inhibit bronchoconstriction have been identified as products of airway epithelial cells. The airway hyperresponsiveness observed in asthma is associated with damage to this layer and, most likely, the phenomenon occurs because of decreased secretion of such epithelium-derived relaxing factors. In addition, the epithelial ciliary escalator, responsible for the clearance of mucus in the airway, may exhibit impaired efficiency.

This presentation will review these aspects of airway epithelial function and will consider the extent to which inhaled cotton and other organic dusts and their constituents may affect the respiratory tract by damaging these components of the lung's homeostatic mechanisms.

Review

For inhaled material, the airway epithelium is the primary point of contact and it has become evident that consequent damage to the epithelial cells may result. This can lead to a number of characteristic effects e.g. hyperresponsiveness.

The airway epithelium exercises several functions of which protection (the wrapping phenomenon) is the most obvious. This it achieves largely by acting as a barrier to diffusion. When the epithelium is damaged, inhaled agents reach the underlying smooth muscle more easily. Thus allergens, dusts, irritants and gases may evince increased effectiveness. The epithelial cells also act to protect sensory nerves involved in neuropeptide release and when damage of this layer occurs reflex bronchoconstriction may be induced.

A further important function of the airway epithelium is that it acts as a site of metabolism. For example, these cells contain diamine oxidase which metabolises histamine and neutral endopeptidase which hydrolyses neuropeptides (Folkerts and Nijkamp 1998). It is now clear that acetylcholine is synthesized in and released from airway epithelial cells (Reinheimer et al 1998; Wessler et al 1998) in addition to being metabolised at this site. It appears that acetylcholine is of central importance in "cross talk" between the many aiway cells e.g. epithelial, smooth muscle, glandular and neuronal (Wessler and Kirkpatrick 1999). This is indicative of a complex network of control of airway functions in which the epithelium acts as a paracrine organ. In the light of these considerations, it is clear that dysfunction or damage of the epithelial layer leads to changes in transmitter and other mediator homeostasis which will affect airway function.

Closely related to the latter is the recognition that the aiway epithelium has an important secretory function. The secretion of mucus is a well-documented example of a contribution to the protective wrapping of the airway lining. It is also clear that inhalational insults may disrupt this regulated secretion giving rise to marked respiratory problems.
The epithelium also synthesises many cytokines and chemokines that are important cell signalling molecules for protective reactions. Dysfunction of the epithelium could therefore compromise the lung's defences to inhaled noxious agents.

In the normal human lung, the basal tone of the bronchus is maintained by a balance between cyclo-oxygenase and 5-lipoxygenase products formed by the epithelium (Watson et al. 1997). This is consistent with the metabolism of arachidonic acid by airway epithelial cells (Holtzman et al. 1994).

The airway epithelium also synthesises endothelin (Mullol et al. 1996). This molecule can cause a marked contraction in epithelium-denuded smooth muscle and a role is proposed for endothelin in modulating airway responsiveness and asthmatic reactions (Chalmers et al. 1997; Hay et al 1993).

Also of great importance is the recognition that this wrapping layer of the lung is responsible for the synthesis and release of epithelium-derived relaxing factors. Prostaglandin E_2 and nitric oxide (NO) have been identified as the main (or only?) players. Their function appears to be protection of the airway from excessive bronchoconstriction (Folkerts and Nijkamp 1998). Conversely damage of the airway epithelium is expected to result in a decrease in the release of these relaxing factors leading to excessive bronchoconstriction. There is accumultating evidence that hyperresponsiveness of the airway in both animal models and human asthma is associated with epithelial damage and decreased secretion of epithelium-derived relaxing factors (Folkerts and Nijkemp, 1998).

However, the effect of NO on airway function in man appears to be complex. In some situations NO may be considered as a toxicant. Thus in inflammatory states, superoxide is potentially available for reaction with NO to yield the peroxynitrite anion. The latter has been shown in animal models of lung inflammation to cause airway epithelial damage, eosinophilia and hyperresponsveiness (Sadeghi-Hashjin et al. 1996).

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It is evident from the foregoing that the airway epithelium is more than a mere wrapping and that its dysfunction or destruction (the wrecking) is likely to have adverse consequences. The following highlights some examples where inhaled agents have been shown to have an adverse impact on this cellular layer of the airway.

There is evidence that organic dusts or their aqueous extracts cause airway epithelial perturbation. Thus for the byssinogenic dusts of cotton, flax and hemp, incubation of normal human nasal epithelium with their extracts leads to disruption of ciliary function and considerable structural damage to the epithelial cells (Wilson et al. 1990). Exposure of guinea pigs to an aerosol of aqueous cotton dust extract results in an increase permeability of the airway epithelium (Bates et al. 1995). As there does not appear to be any marked histological change to the cells at this level of exposure, it may be considered that the dust challenge has resulted in disruption of the tight inter-cellular junctions. In vitro studies with human bronchial epithelium (Palmberg et al. 1998) have demonstrated that swine environment dust is a strong stimulus for the production of the cytokine, IL8. This action is independent of lipopolysaccharide (LPS).

Evidence is collecting (Tomee et al. 1998) that various inhaled allergens, notably the house dust mite antigen, can induce expression of proteolytic enzymes in the airway epithlelium and this leads to pro-inflammatory cytokine release and cell detatchment.

Non-specific/defined exogenous inhaled particles also appear to affect the epithelium directly, especailly in the overload situation when macrophages are unable to cope with a massive particulate insult (Chung et al. 1996). In this situation, such particles are ingested by several types of the airway epithelium cells (type I cells > type II cells > mucuous cells). It is probable that this uptake contributes to the eventual development of pulmonary fibrosis. For particles containing iron, reactive oxygen species appear to be involved in the uptake.

For inhaled toxic gases such as ozone and nitrogen dioxide, there is evidence that cytokine release from the airway epithelium is an early event (Mogel et al. 1998). In the case of ozone, cytokines and other products released from the epithelium appear to interact with other cell types of the underlying tissues, such as the endothelium, to orchestrate inflammatory and immune responses. It has also been found that the ozone-induced increase in the permeability of the tracheal mucosa is via a neuropeptide-dependent mechanism (Nishiyama et al. 1998).

In various occupational and environmental settings, metals either as vapour or particulates may be inhaled with toxic consequences. It has recently been shown that arsenic and vanadium may cause lung damage by inducing the expression of mitogen-activated protein kinases in bronchial epithelial cells and this leads to the synthesis of inflammatory proteins (Samet et al. 1998). In vivo studies in habitual smokers of marjuana, cocaine and tobacco (Barsky et al. 1998) suggest that these inhaled materials or their combustion products exert a cancerization effect on the bronchial epithelium.

Regarding other insoluble particles, Marks-Konczalik et al (1998) have shown that crocidolite and silica are cytotoxic to the airway epithelium via a pro-oxidant mechanism. However, rockwool fibres are not cytotoxic because they induce the expression of a manganese-dependent superoxide dismutase in the airway epithelial cells.

Returning to organic dusts, there is accumulating evidence that various components of these heterogenous materials have the potential for adversely affecting the respiratory tract epithelium.

LPS is one of the most potent biologically active molecules known and several studies indicate an effect on the epithelium. Inhalation of LPS by the guine pig causes rapid and marked destruction of this cellular alyer (Davey and Nicholls, 1994a). These changes eppear to be associated with airway hyperresponsiveness and inflammation (Young et al. 1994; Davey et al. 1994b). More recently Peralta and Casale (1998) have found that LPS-induced neutrophil transmigration in the lung is dependent on LPS-induced protein synthesis in the airway epithelium. LPS also enhances neurogenic plasma exudation by augmenting the responses to tachykinins partly through NK-1 receptors to directly increase vascular permeability (Kuo et al. 1998).

The recent interest in the 1-3bD-glucans as important components of organic dusts and various indoor air environments has lead to an examination of their effects on airway function. The results in this meeting, presented by Jones and Nicholls, indicate that a baker's yeast glucan can release a factor from the airway epithelium of the guinea pig that reduces the sensitivity of the lung to bronchoconstrictor agents. A role for PGE_2 release is proposed.

In the case of cotton dust, bract-derived tannins have been proposed as important aetiological agents of byssinosis (Rohrbach, 1991) and in vitro studies have demonstrated that this group of substances can inhibit the electrophysiological properties of tracheal epithelial cells resulting in inhibition of chloride secretion (Cloutier and Rohrbach, 1986). In addition, an aminopolysaccharide protein complex extract from cotton dust has also been shown to adversely affect epithelial development in explants of human foetal bronchial tissue (Nicholls et al. 1983).

Conclusion

In conclusion, this brief survey, which updates an earlier review (Turner & Nicholls, 1995), indicates the importance of the airway epithelium in lung homeostasis. It is evident, that when assaulted by an inhalation challenge of a noxious agent, the adverse impact on the epithelium has the propensity for subsequent and down-stream elaboration to threaten normal function. The selected examples of inhaled environmental materails show evidence for the pivotal role of the epithelium as a first point of contact and effect. It is thus an important target site for study by all who wish to elucidate the effects of inhaled materials on the airway.

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