Reviews in Medicine

Recent advances in asthma

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Introduction

There have recently been important advances in our understanding of asthma mechanisms and treatment. Asthma is now recognized as a disease of the airways which involves a special type of inflammation, characterized by the presence of activated mast cells, eosinophils and T-lymphocytes. There has been a growing recognition that chronic rather than acute inflammatory events are more relevant to understanding the underlying mechanisms in asthma and the role of cytokines, as mediators of chronic inflammation, has been an area of very rapid development. At the same time the approach to asthma treatment has changed, with a much greater emphasis on the earlier and more widespread use of inhaled anti-inflammatory drugs, and particularly inhaled steroids. There has also been an increased understanding of the mechanisms of action of existing anti-asthma therapies, but at the same time questions have been raised about the safety of some treatments. This has prompted the search for novel anti-asthma therapies, based on our current understanding of pathophysiological mechanisms. The literature on asthma is vast and we do not intend to provide an exhaustive or comprehensive review, but have concentrated on some areas where there have been advances in knowledge which have clinical and therapeutic relevance.

Epidemiology

Asthma is one of the commonest diseases in industrialized countries and has a large economic impact in terms of health costs and loss of time from work. The total costs for asthma in the USA were recently estimated as $6.2 billion, representing 1% of all US health care costs.1 There have recently been several studies which indicate that the prevalence of asthma has increased over the last few years.2 A study in Finnish army conscripts has revealed a marked increase in the number of recruits with a diagnosis of asthma.3 In the UK there is evidence for similar trends.4 Admission of children to hospital with asthma attacks has more than doubled over the last 10 years in the UK.5 The reasons for this increase in morbidity are uncertain, since it is difficult to identify a single factor in the environment which has changed over the same time frame. There has been concern about air pollution, but little direct evidence to link specific changes in air quality to worsening of asthma.6 It is likely that an interaction between different air pollutants is important. A recent study investigated whether a common air pollutant, ozone, had any influence on allergen challenge in a group of mild asthmatic patients. A concentration of ozone as low as 0.12 parts per million, which itself had no effect on airway function, led to an increase in both the early and late response to inhaled allergen.7 Nitrogen dioxide (NO2) is a pollutant which is particularly associated with car exhaust fumes but there are few studies which have examined its airway effects or whether it interacts with other air pollutants or with allergen.

Allergen exposure is probably the most important factor in determining asthma severity. Exposure to allergen in early life is an important risk factor in the subsequent development of asthma. There is a striking association between the dust levels of Der p1 (the major allergen of house dust mite) at the time of birth and the prevalence of asthma at 11 years of age,8 although current levels of exposure may have been a confounding factor in this study. Increased allergen exposure has been implicated in the increase in asthma and the ‘tight’ houses, with poor ventilation and central heating increasingly found in temperate climates, may increase the house dust mite population and the concentration of indoor pollutants such as cigarette smoke.9
Another possible factor contributing to the increased morbidity and even mortality of asthma may be the use of anti-asthma medication, and in particular the excessive use of inhaled β-agonists.

The pathology of the asthmatic airway mucosa

Early studies in patients dying from status asthmaticus revealed marked inflammation of the bronchial tree. Recent evidence using fibreoptic bronchoscopy and biopsy has confirmed that similar changes are also present in asthmatic patients during life. There is extensive damage of the epithelium; the numbers of epithelial cells recovered by bronchoalveolar lavage correlate with the extent of airways hyperresponsiveness. Recent morphological studies using transmission electron microscopy and the use of monoclonal antibodies to differentiate collagen subtypes, have shown that bronchial epithelial basement membrane is of normal thickness in asthma. However, there is a dense deposition of collagen fibres in the subepithelial region. This consists predominantly of collagen types 3 and 5, together with fibronectin but not laminin. The cellular source of the subepithelial collagen may be the myofibroblast.

Mast cells

Mast cells in the asthmatic airway mucosa are degranulated. Considerable interest has centred upon the recent observation that rodent mast cells synthesize a wide range of cytokines upon IgE-mediated activation. There is, as yet, limited data on the generation of cytokines for human mast cells. Steffen et al. reported the presence of tumour necrosis factor α (TNFα) in mast cells/basophils derived from the culture of human bone marrow. Preliminary data suggest that purified human pulmonary mast cells contain TNFα bioactivity.

Eosinophils

Increased numbers of eosinophils in asthmatic airways is an almost constant finding. The eosinophils are also activated and their state of activation and numbers correlate with airways hyperresponsiveness. Eosinophil-derived proteins such as major basic protein, in the sputum correlate with disease activity and the levels decrease after appropriate treatment. Eosinophil cationic protein (ECP), which is located in the eosinophil granule matrix, is also raised in serum after allergen-provoked asthma and during the pollen season in atopic individuals. Eosinophil precursors increase during the late asthmatic reaction and their numbers fluctuate in relation to season exposure in atopic subjects. This suggests that exposure to allergen stimulates eosinophil production by the bone marrow.

Macrophages and monocytes

Immunohistochemistry of bronchial biopsy specimens shows that the submucosa had a significantly increased macrophage population in asthmatic patients. The population had phenotypic characteristics of peripheral blood monocytes, suggesting that they had migrated recently into the lung. HLA Class II antigen was expressed on the infiltrating cells of the airway mucosa to a greater extent in asthmatic subjects than in normal individuals. The major activity secreted by peripheral blood monocytes and alveolar macrophages which augment eosinophil survival and increase their capacity to produce proinflammatory mediators is granulocyte-macrophage colony stimulating factor (GM-CSF).

Lymphocytes

There is a tendency for increased numbers of T cells in asthmatic airway biopsies, with an increase in the numbers of cells expressing receptors for interleukin-2 receptor (CD25), reflecting lymphocyte activation. The numbers of CD25+ cells correlated with airways hyperresponsiveness. Hamid et al. using the technique of in situ hybridization to examine expression of interleukin (IL)-5 in bronchial biopsies, demonstrated increased IL-5 mRNA in the bronchial mucosa of six out of 10 asthmatic subjects and in none of the nine controls. Although the number of patients studied was small, there was a trend for the IL-5+ asthmatic subjects to have more severe asthma than those in whom no significant IL-5 was observed. Biopsies positive for IL-5 mRNA also had a greater number of CD25+ cells, a greater number of eosinophils and a greater number of EG2+ eosinophils (which stains for the secreted form of an eosinophil granule protein). These data are consistent with the suggestion that IL-5, secreted by activated T lymphocytes, contributes to the recruitment and activation of eosinophils in the bronchial mucosa in asthma.

The murine equivalent of TH2-type cells which produce IL-4 and IL-5 (as compared to TH1-type cells which generate IL-2 and gamma-interferon) have also been observed in the bronchial mucosa and bronchoalveolar lavage fluid from mild atopic asthmatics. By immunomagnetic enrichment, the IL-4+ and IL-5+ cells were entirely in the CD2+ population. The numbers of activated T cells and their products correlate with the severity of disease.

In chronic to severe corticosteroid-dependent
asthma, activated T cells appear in peripheral blood and their numbers decrease after steroid treatment. In contrast, there is a group of steroid-resistant individuals who have chronically activated CD4+/CD25+ cells which proliferate in vitro, even in the presence of dexamethasone. A recent placebo-controlled, double-blind trial of cyclosporin A in chronic steroid-dependent asthma showed efficacy with a substantial increase in lung function. Taken together, these studies suggest that T cell-mediated responses, independent of IgE production, are important regulatory pathways of the pathogenesis of airways inflammation.

Cytokines

Now that asthma is seen as a chronic inflammatory disease understanding the role of cytokines in orchestrating the chronic eosinophilic inflammation is an important research goal. It is now clear from a number of different studies that asthma, even in its mildest form, is characterized by local infiltration of inflammatory cells in which mononuclear cells and eosinophils are particularly prominent. The mechanism for the selective eosinophilic accumulation is unknown. Although mast cell mediators may contribute to eosinophil recruitment, there is increasing evidence that cytokines may play an important role in the recruitment and activation of these effector cells.

For example, IL-3, is a mast cell growth factor and stimulates proliferation of eosinophils from bone marrow stem cells. IL-3, IL-5 and GM-CSF promote maturation and differentiation of eosinophils. They also prolong eosinophil survival in culture and, presumably, persistence of eosinophils from tissues. This may be achieved by inhibition of programmed cell death (apoptosis) in eosinophils. T cell-derived lymphokines, IL-4 and gamma-interferon are involved in the regulation of IgE production.

The T lymphocyte is not the only cell which produces cytokines. There is now increasing data to indicate the eosinophils, fibroblasts and epithelial cells can also secrete cytokines. Of particular note is the finding that eosinophils themselves can express genes for cytokines and release active molecules, such as IL-1, GM-CSF, transforming growth factor α (TGFα) and TGFβ-1.

Adhesion molecules

Adhesion molecules on inflammatory cells and endothelial cells play a critical role in inflammatory cell recruitment. Thus cytokines may lead to selective eosinophil accumulation via enhanced recruitment through the induction of selected adhesion molecules on endothelial cells. IL-5 selectively enhances the in vitro adhesion of eosinophils to endothelium. Of the three major cytokine-induced endothelial adherence molecules, intercellular adhesion molecule-1 (ICAM-1), endothelium-leukocyte adhesion molecule-1 (ELAM-1) and vascular cell adhesion molecule-1 (VCAM-1) that have been characterized and identified which may be important in leukocyte adhesion, VCAM-1 appears to have selectivity for the eosinophil.

Specific anti-VCAM-1 antibody-inhibited eosinophil, but not neutrophil adherence. A counter ligand for VCAM-1 is VLA-4, one of the β1 integrin adhesion molecules also referred to as CD49/CD29. Neutrophils do not show evidence of VLA-4, whereas eosinophils and basophils both expressed VLA-4. IL-4 selectively induces VCAM-1 expression and VLA-4 has been shown to increase adhesiveness in endothelial cells for eosinophils and basophils, but not neutrophils. The VLA-4 molecule can also function as an alternative receptor for fibronectin and eosinophils also express VLA-6 which binds laminin. Thus, the ability of eosinophils to remain localized within the extravascular inflammatory site may be increased in tissues expressing higher levels of laminin and/or fibronectin.

The role of adhesion molecules in asthma was strongly supported by evidence from Wegner and colleagues who identified the relationship between eosinophil infiltration and airways responsiveness in the primate model of asthma. The administration of anti-ICAM-1 monoclonal antibody in vivo reduced eosinophil infiltration in airways hyperresponsiveness following antigen inhalation challenge. The type of response in the airways was dependent upon the model employed. When a subset of intrinsically hyper eosinophilic animals were given a single inhaled allergen challenge, there was both an immediate and a delayed asthmatic response. The latter was associated with a neutrophil influx into the airways and an associated airways hyperresponsiveness which was inhibited by anti-ELAM-1 but not anti-ICAM-1.

The beta agonist debate

Inhaled β2-adrenoceptor agonists are by far the most effective bronchodilators currently available and their use has increased dramatically in recent years throughout the world.

Mechanism of action

The molecular mechanism of their bronchodilator action has recently been elucidated; although several effects of β-agonists have been described,
the most important mechanism of action involves activation of a large conductance calcium-activated potassium channel (known as the maxi-K channel), which is blocked by the scorpion venom toxin charybdotoxin. Charybdotoxin blocks the bronchodilator action of β-agonists in both animal and human airways,3,34 and there is recent evidence that the β2-receptor in airway smooth muscle cells is directly coupled via a stimulatory G-protein (Gαs) to the maxi-K channel, without the involvement of the second messenger cyclic AMP.55 There has been considerable debate about the non-bronchodilator/anti-inflammatory effects of β-agonists. β-Agonists are effective in inhibiting microvascular leakage and plasma exudation in the airways,36,57 and inhibit mast cell mediator release. In this respect they could be considered as anti-inflammatory agents, but they do not seem to have effects on the chronic inflammatory process and therefore do not have steroid-like actions. This is shown most directly by the lack of effect of treatment with a regular inhaled β-agonist on the inflammatory cell profile in bronchial biopsies taken from asthmatic patients, whereas inhaled steroids are very effective in suppressing the inflammatory response.58 Similarly the new long-acting inhaled β-agonist salmeterol has no effect on the profile or activation of inflammatory cells in biopsies of asthmatic patients.59 Clinical evidence that this is so is provided by a study which compared regular inhaled β-agonist with regular inhaled steroids over a 2 year period in over 100 newly diagnosed patients.60 There was a marked difference between the two groups with more frequent symptoms and use of rescue bronchodilators, greater diurnal variability and greater airway responsiveness in the group treated with β-agonists alone.

**Questions about safety**

Although β-agonists are highly effective as bronchodilators, questions have recently been raised about their long-term safety in asthma when used on a regular basis.61 Epidemiological studies in New Zealand suggested that there may be a link between the use of a particular β2-agonist fenoterol and the risk of asthma death. The original study was criticized because of the matching of controls but a further study which took this into account still showed an association.62 An epidemiological study in the Province of Saskatchewan in Canada examined the link between death and near death from asthma and the use of anti-asthma medication obtained from computerized records over a 7 year period.63 There was a significant association between asthma death and near death and the regular use of inhaled β-agonists, with a very steep dose–response relationship. The risk associated with fenoterol was significantly greater than the risk attached to salbutamol, but fenoterol is approximately twice the strength of salbutamol compared puff for puff.64 Correction for the bronchodilator dose given inhaled fenoterol and salbutamol approximately equal risk. The most likely explanation for this association between high doses of β-agonists and asthma death would be that the high use of a β-agonist inhaler is an indication of severe asthma, giving a higher risk of death. While this is certainly a factor, adjustment for all possible markers of severity fails to alter the association between β-agonist use and risk of death and near death.65 Furthermore there is no such association between mortality and the use of inhaled steroids, which would also be used in patients who may have moderately severe asthma. This suggests (but cannot prove) that there may be a causal link between β-agonist inhaler usage, especially in high doses, and the risk of death or near death from asthma.

Studies have also indicated that β-agonist may be contributing to an increase in asthma morbidity. A widely quoted cross-over study carried out in New Zealand found that regular use of inhaled fenoterol (four times daily) was associated with worse control of asthma (judged by combined symptom scores, peak flow measurements and airway responsiveness) compared with the period when patients took fenoterol on an 'on demand' basis.66 Two studies from Holland indicate that this may not be confined to fenoterol, since regular doses of inhaled salbutamol increase (albeit to a small extent) airway responsiveness, whereas when salbutamol was taken as required to did not.67 Over a 2 year period regular, but not on demand salbutamol, is associated with an increased annual decline in spirometric values,68 although a similar accelerated fall in lung function is also seen with ipratropium bromide, so the phenomenon may apply to all bronchodilators. These studies have raised concerns, although the Committee of Safety on Medicines has looked at all currently available evidence and is of the opinion there is no cause for concern.69 It is obviously important that further carefully controlled studies are carried out, particularly since long-acting inhaled β2-agonists have now been introduced (see later). A Task Force has recently been established by the National Asthma Campaign which includes a Working Party on Therapy which will examine some of these issues.70

**Mechanism of adverse effects**

Since β-agonists have been implicated in asthma mortality and morbidity, several possible mechanisms have been proposed. The link between β-agonists and sudden death from asthma has been attributed to cardiac arrhythmias induced by β-
agonists, particularly in the presence of hypo-
kaeaemia and hypoxia, yet there is little direct
evidence for this. In a recent series of 'near deaths'
from asthma there was no evidence for any cardiac
arythmias.71 In a recent study it was found that an
inhaled β-agonist protects against induced broncho-
constriction up to a point, but at high doses
protection is lost and the airway function falls even
more precipitously.72 This may indicate that
inhaled-β agonists provide effective protection
against day-to-day constrictor stimuli, but that
large constrictor stimuli (e.g. massive allergen
exposure or upper respiratory tract viral infection)
may lead to a sudden, and possibly catastrophic,
fall in lung function.

The effect of β-agonists on asthma morbidity
may relate to the fact that β-agonists control
asthma symptoms without controlling the underly-
ing chronic inflammation so that patients may fail
to take regular inhaled anti-inflammatory treat-
ments. β-Agonists may paradoxically increase air-
way hyperresponsiveness in asthmatic patients,
and there may be a rebound increase in respons-
iveness when β-agonists are stopped.61 Another
hypothesis is that β-agonists inhibit the release of
mediators such as heparin from mast cells, since
heparin may have anti-inflammatory properties,73
although the amount of heparin which is released
from mast cells is likely to be very low. Other
theories suggest that increased viscous mucus
secretion may be a factor, whereas others suggest
that the bronchodilator response to β-agonists
allows more allergen to be inhaled into the lower
airways where a chronic inflammatory response is
initiated.74 In studies in guinea pigs the non-
bronchodilating (+) enantiomer of β-agonists
may increase airway responsiveness, suggesting
that the normal racemic (±) β-agonists such as
salbutamol, terbutaline and fenoterol may be
deleterious,75 although whether these considera-
tions are clinically relevant remains to be deter-
mined. The clinical implication of these studies is
that short-acting inhaled β-agonists should only be
used on demand for symptom control and should
never be used on a regular basis. In patients who
are taking high doses of inhaled β-agonists anec-
dotal reports suggest that there may an improve-
ment in asthma if β-agonist inhaler use is
restricted.76

Inhaled steroids

Efficacy

There is little doubt that inhaled steroids are
currently the most effective therapy available for
asthma. In several countries, guidelines to asthma
therapy have been drawn up74–79 and recently
international guidelines have been published.80 All
of these guidelines stress the introduction of
inhaled anti-inflammatory treatment at an early
stage and in adult steroids are the preferred
therapy. Several studies have now demonstrated
convincingly that inhaled steroids taken over a
long period will resolve or substantially suppress
the inflammatory changes in the Airways associated
with asthma.58,81–84 Steroids are very effective in
controlling the inflammation in asthma, but when
steroids are withdrawn asthma symptoms, Airways
hyperresponsiveness (and presumably inflam-
mation) return.85

The molecular mechanisms of action of steroids
in asthma are still not certain, but are likely to
involve an effect at the gene transcription level and
particularly on the transcription of critical
cytokines such as IL-3, IL-5 and IL-6.86,87 Cor-
ticosteroids inhibit the survival of eosinophils
in response to GM-CSF and IL-5.35,88 An additional
direct interaction between the occupied glucocor-
ticoid receptor and the transcription factor
activator protein-1 which may be switched on in
inflammation has also been described.89 In addition
to their inhibitory actions on inflammatory cell
infiltration and activation steroids may have a
direct inhibitory effect on airway microvascular
leakage90 and on airway mucus secretion.91 This
broad spectrum of effects of corticosteroids on
inflammatory cells may explain the efficacy of this
form of medication in chronic asthma.

Steroid-resistant asthma

Corticosteroid resistance in some patients with
asthma has been recognized for many years, but the
mechanisms are far from clear. The importance
of this phenomenon is that it may provide important
clues to understanding the mechanism of action of
corticosteroids in asthma. One action of steroids is
to increase the synthesis of lipocortin-1 which has
some anti-inflammatory effects. Two studies have
demonstrated that antibodies to lipocortin-1 are
not elevated in steroid-resistant asthmatic.92,93
There is evidence that T-lymphocytes show
reduced responsiveness to steroids in vitro which is
correlated with reduced in vivo responsiveness.94
This does not appear to be due to a defect in steroid
binding to the glucocorticoid receptor,95 but a
defect in binding of the activated steroid receptor
to steroid responsive elements on target genes has
not been excluded. The defect in steroid responsiv-
ness is also seen in monocytes from these patients.96
The reduced responsiveness is not confined to
inflammatory cells since there is evidence for
reduced skin blanching response to steroids in such
patients.97
Safety issues

As steroids are used at an earlier stage in therapy and larger inhaled doses are available there are an increasing number of reports about systemic side effects of inhaled steroids.98 These side effects include easy bruising and skin thinning99 reduced bone density,100 biochemical markers of increased bone metabolism101-104 and cataracts.105 It is difficult to evaluate the importance of these changes since the patients have usually also taken courses of oral steroids. It is not yet clear whether sensitive biochemical indices of bone metabolism such as serum osteocalcin indicate a long-term effect on bone structure, however. At daily doses of 800 μg or less, systemic effects are uncommon with either beclomethasone dipropionate (BDP) or budesonide. There may also be inter-individual susceptibility to systemic effects.106 Systemic effects of inhaled steroids arise from the gastrointestinal absorption of the fraction of inhaled steroid which is swallowed after oropharyngeal deposition, and from the fraction absorbed from the lower respiratory tract. Oropharyngeal deposition is reduced by the use of a large volume spacer and therefore systemic effects may be reduced.107,108 Mouth washing has a similar (but lesser) beneficial effect.109 Budesonide is more efficiently degraded by hepatic metabolism than BDP and therefore the fraction absorbed from the gut is less likely to reach the systemic circulation. There is some evidence that at high doses systemic effects of inhaled budesonide are less than those of BDP at high doses,104 but the appropriate long-term comparative studies in asthmatic patients have not yet been done. There has been particular concern about the effect of inhaled steroids on growth in children. A sensitive measurement of growth may be the length of the lower leg measured by kmometry. With this technique it has been observed that a daily inhaled dose of 800 μg budesonide and 400 μg BDP have an inhibitory effect, whereas 400 μg budesonide does not.109,110 This is a very sensitive technique since 2 mg prednisolone orally has an even greater suppressive effect, yet it is known that such a dose of oral steroids does not affect overall height of children. These studies indicate that it is important to use as low a dose of inhaled steroids as possible in controlling asthma, and to minimize systemic effects by using a large volume spacer and by mouth rinsing when high doses are required.

New anti-asthma drugs

Although no new classes of anti-asthma drug have yet reached the clinic, several drugs are in clinical development and there have been improvements in existing classes of drug.111

Long-acting inhaled β2-agonists

Inhaled β2-agonists with a long duration of action, such as salmeterol and formoterol, which give bronchodilatation and protection against bronchoconstriction for over 12 hours have recently been introduced.112 Clinical trials show that both of these long-acting β2-agonists are highly effective in controlling chronic asthma, have no significant side effects and (perhaps surprisingly) tolerance does not develop.113 These drugs are effective in controlling nocturnal symptoms.114 There is little to suggest that these drugs have any anti-inflammatory effect which is different from short-acting β-agonists and the protective effect against the late response to allergen and subsequent airway hyper-responsiveness,115,116 is likely to be explained by functional antagonism. The exact place of long-acting β2-agonists in the management of asthma is still not certain, but it is probably wise to administer them only in combination with inhaled steroids.

Selective phosphodiesterase inhibitors

By inhibiting the breakdown of cAMP by phosphodiesterase (PDE), it should be possible to increase intracellular concentrations and thereby relax airway smooth muscle and also potentiate the bronchodilator effect of β-agonists. It is now recognized that there are several isoenzyme families of PDE and several selective inhibitors have recently been developed.117,118 The isoenzymes which are involved in relaxation of airway smooth muscle (types III and IV) make up <5% of the total enzyme activity.119 Selective inhibitors of these isoenzymes, such as SK&F 94836 which inhibits type III isoenzyme, may therefore be useful as bronchodilators. Evidence now suggests that PDE IV may be important in inflammatory cells such as mast cells, eosinophils, macrophages and lymphocytes,118,120 and that PDE IV inhibitors, such as rolipram and denbufylline, may be useful anti-inflammatory drugs in asthma. Drugs which inhibit both PDE III and PDE IV enzymes, such as AH 21-132 (benzafentrine) and zardaverine,121,122 may be both bronchodilator and anti-inflammatory, and are therefore of particular interest for future development. The main problem with PDE inhibitors appears to be the profile of side effects. PDE III inhibitors are associated with cardiovascular side effects, whereas the major problem with PDE IV inhibitors is nausea and vomiting.

K+ channel openers

K+ channels play an important role in the recovery of excitable cells after activation and in maintaining cell stability. Opening of K+ channels therefore
results in relaxation of smooth muscle and inhibition of secretion. Many different types of K⁺ channel have now been recognized electrophysiologically and with several selective toxins and drugs.¹²³ Drugs which selectively activate a K⁺ channel in smooth muscle, such as BRL 34915 (cromakalim), have been developed for the treatment of hypertension. These drugs inhibit spontaneous and induced tone in airway smooth muscle in vitro and might, therefore, have a role in normalizing ‘hyperreactive’ airway smooth muscle. K⁺ channel activators are currently under investigation as potential anti-asthma compounds.¹²⁴ The active enantiomer of cromakalim, BRL 38227 (lemakalim), is a relatively effective relaxant of human bronchi in vitro and appears equally active against several spasmodgens.¹²⁵ In vivo it has no bronchodilator effect or protective effect against bronchoconstrictor challenge at maximally tolerated oral doses,¹²⁶ but cromakalim has been shown to have a small protective effect against the fall in lung function at night in asthmatic patients.¹²⁷

Side effects include headache, flushing and postural hypotension, due to vasodilatation. It will therefore be necessary to develop these drugs for inhalational use in order to avoid these effects, although it may be possible to develop K⁺ channel openers which are more selective for airway than vascular smooth muscle, in view of the diversity of K⁺ channels. One such airway selective K⁺ channel opener (BRL 55834) has already been described.¹²⁸ The future success of these compounds in asthma will probably depend on whether they have any additional effects not shared with β-agonists. K⁺ channel activators inhibit the release of neuropeptides from sensory nerves and modulate neurotransmission in the airways,¹²⁹ but whether they have effects on inflammatory cells is not certain. Many different types of K⁺ channel have now been characterized; cromakalim and related drugs appear to open a low affinity ATP-dependent channel (which opens in response to a fall in intracellular ATP concentrations). The K⁺ channel involved in airway smooth muscle relaxation³³,³₄ and neuromodulation of airway nerves³⁰,³¹ is the maxi-K channel, but no openers of this channel have so far been identified.

Mediator antagonists

Many different mediators are implicated in the pathophysiology of asthma and it is therefore somewhat unlikely that blocking the effects of a single mediator would have a major clinical impact. Antihistamines have minimal effects in asthma and are not useful in therapy,¹³² but recently lipid mediators have received more attention. Several potent leukotriene, PAF and thromboxane antagonsists have now been developed and are currently undergoing clinical trials in asthma. Initial results appear to suggest that potent leukotriene antagonists, such as MK-571, ICI 204,219 and SKF 104,353, have a significant protective effect against some constrictor challenges, such as exercise, allergen and aspirin.¹³³-¹³⁶ and long-term clinical trials are now underway, with preliminary encouraging results.¹³⁷ Although AHP has several properties which suggest that it may play an important role in asthma, but recent preliminary studies with potent PAF antagonists show no effect on allergen challenge.¹³⁸-¹⁴⁰ Similarly thromboxane receptor antagonists have proved disappointing.¹⁴¹

Enzyme inhibitors

An alternative to antagonists of mediator receptors are drugs which inhibit the enzymes involved in mediator synthesis. 5-Lipoxygenase (5-LO) is the critical enzyme involved in the generation of leukotrienes. Several drugs have been developed which inhibit 5-LO, although most of these compounds are very weak. Thus zileuton, the most effective of these drugs available for clinical use, has only a trivial inhibitory effect on allergen-induced responses and leukotriene production,¹⁴² although it has proved to be more effective in some other challenges.¹⁴³ Zileuton, as most other 5-LO inhibitors, appears to work as a redox inhibitor of the enzyme, but more recently a novel inhibitor MK-886 has been developed, which appears to bind to a 5-LO activating protein (FLAP) in the cell membrane, to which cytosolic 5-LO must bind in order to be active.¹⁴⁴,¹⁴⁵ There is a theoretical advantage to the use of 5-LO inhibitors compared with leukotriene antagonists since the formation of LTBi and other 5-LO products, as well as sulphidepeptide leukotrienes will also be inhibited.

Inhibitors of neurogenic inflammation

Neuropeptides, which may be released from sensory nerves in airways in asthma via an axon reflex might amplify the inflammatory response. There are several approaches to inhibiting these local reflexes.¹⁴⁶ Antagonists of sensory neuropeptides, such as substance P, neuropeptide A and calcitonin gene-related peptide, are currently under development. Most of the inflammatory effects of tachykinins are mediated by NK₁-receptors and several selective antagonists have been developed. A potent non-peptide NK₁-antagonist, CP 96,345, has recently been discovered, which may prove to be a very useful lead compound which avoids all the problems associated with the development of peptide antagonists.¹⁴⁷ This antagonist is extremely effective in blocking the inflammatory effects of
tachykinins released endogenously by nerve stimulation.\textsuperscript{148} Another approach is to inhibit the release of these peptides from C fibres than to block their effects, since several peptides are likely to be released from sensory nerves. Opioids markedly inhibit sensory neuropeptide release and have been shown to block neurogenic plasma exudation, mucus secretion and bronchoconstriction in guinea pigs and neurogenic mucus secretion in human airways.\textsuperscript{149} Several other agonists inhibit neuropeptide release, including \(\alpha_2\)-agonists, gamma-amino-butyric acid, and histamine \(H_1\)-agonists, which all appear to open a common \(K^+\) channel which is blocked by charybdotoxin.\textsuperscript{150}

**Frusemide**

Inhaled frusemide protects against "indirect" bronchoconstrictor challenges, such as exercise, fog, allergen, sodium metabisulphite and adenosine, but has no effect against direct bronchoconstrictor challenges such as histamine, methacholine and PGE\(_2\).\textsuperscript{130} These effects mimic those of sodium cromoglycate but, in addition, inhaled frusemide inhibits certain types of induced cough.\textsuperscript{151} The mechanism of action of frusemide in asthma is not certain, but it is ineffective systemically, suggesting that it is acting at the airway surface. Frusemide works as a diuretic by inhibiting the \(Na^+\)/\(K^+\)/\(Cl^-\) cotransporter in renal tubular cells, but the more potent inhibitor bumetanide is ineffective in the same challenges.\textsuperscript{152} Some effects of frusemide are mediated by the release of PGE\(_2\), but cyclooxygenase inhibition does not abolish the anti-asthma effect. The most likely possibility is that frusemide blocks a certain type of \(Cl^-\) channel which is necessary for the activation of inflammatory cells and sensory nerves.

**Immunomodulators**

T-lymphocytes may play a critical role in initiating and maintaining the inflammatory process in asthma via the release of cytokines. Methotrexate has a steroid-sparing effect in asthma, probably acting as a non-specific immunosuppressive or anti-inflammatory agent.\textsuperscript{153,154} The side effects of methotrexate (particularly nausea and blood dyscrasias) preclude its use in all but the most severe asthmatic patients who have problems with oral steroids.

More specific immunomodulators, such as cyclosporin A, which have an inhibitory effect on T-lymphocyte function, might be more useful in controlling asthma, and there is some evidence that low-dose cyclosporin A improves lung function in steroid-dependent asthmatics.\textsuperscript{32,155} The nephrotoxicity of cyclosporin A would limit its widespread use but derivatives with less nephrotoxicity are now being developed and the possibility of using inhaled cyclosporin is being explored. Other immunomodulators such as FK506 and rapamycin appear to be more potent and less toxic.\textsuperscript{156}

In the future it may be possible to develop more specific inhibitory drugs. There is particular interest in the development of an inhibitor of IL-5 synthesis or receptor antagonist, since blocking IL-5 with a monoclonal antibody appears to inhibit eosinophil infiltration into the airways completely after allergen exposure.\textsuperscript{157} An endogenous IL-1 antagonist (IL-1ra) has recently been cloned, which competes with IL-1 for binding to IL-1 receptors.\textsuperscript{158} This antagonist has an inhibitory effect on the hyperresponsiveness and leukocyte infiltration following allergen challenge in guinea pigs,\textsuperscript{159} suggesting that it may have therapeutic potential in asthma.

**References**

**Epidemiology**


**Inflammatory cells**


**Immunomodulators**


Cytokines


Adhesion Molecules


Beta-agonists


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New drugs


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