New drugs for asthma

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ABSTRACT: Several new drugs are now under development for the treatment of asthma, either as improvements to existing classes of therapy or as novel agents.

Amongst bronchodilators, long-acting inhaled β₂-agonists (salmeterol and formoterol) look very promising and there is also interest in selective phosphodiesterase inhibitors, K⁺ channel-openers and nitrodilators.

There are several new inhaled corticosteroids under development and more selective agents include leukotriene antagonists, 5-lipoxygenase inhibitors, bradykinin and tachykinin antagonists and immunomodulators.

In the future, adhesion molecule inhibitors and cytokine inhibitors may be developed.

There are two main approaches to the development of new anti-asthma treatments: improvement in an existing class of effective drug; or development of novel compounds, based either on rational developments (e.g. mediator antagonists) or from chance observations (e.g. frusemide).

Table 1. – New Bronchodilators

<table>
<thead>
<tr>
<th>Existing</th>
<th>Novel</th>
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<tr>
<td>β₂-agonists: long-acting (salmeterol, formoterol)</td>
<td>VIP/VIP analogues</td>
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<td>Methylxanthines: less side-effects (enprofylline)</td>
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<td>Anticholinergics: more selective (M3-antagonists)</td>
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<td>Nitrodilators (nitroprusside, ANP)</td>
<td>VIP: vasoactive intestinal peptide; ANP: atrial natriuretic peptide.</td>
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β₂-agonists remain the most widely used and effective bronchodilators in clinical practice. They act as functional antagonists and reverse airway smooth muscle contraction irrespective of the spasmogen. They are equally effective on large and small airways, and may have effects on cells other than airway smooth muscle, such as mast cells, to prevent mediator release; also, on microvascular leak and
cholinergic neurotransmission [4]. Many selective β2-agonists are now available and there has been a search for β-agonists which have even greater selectivity for β2-receptors. However, it is unlikely that any greater selectivity would be an advantage clinically, since, when the drugs are given by inhalation a high degree of functional β2-receptor selectivity is obtained. Furthermore, many of the side-effects of β-agonists (tremor, tachycardia, hypokalaemia) are mediated via β2-receptors.

Long-acting β2-agonists. The most important recent advance has been the introduction of inhaled β2-agonists with a long duration of action, such as salmeterol and formoterol, that give bronchodilatation and protection against bronchoconstriction for over 12 h [5]. Clinical trials show that both of these long-acting β2-agonists are highly effective in controlling chronic asthma and have no significant side-effects. Perhaps surprisingly, tolerance does not appear to develop to their bronchodilator action [6, 7], although there is some evidence for tolerance to their protective action against constrictor challenge [8]. It is difficult to imagine that any future drug could be more effective than a β2-agonist as a bronchodilator, but doubts have recently been expressed about the role of inhaled β2-agonists in the control of asthma [9]. Regular use of inhaled β2-agonists appears to give worse control of asthma than the use of β-agonists "on demand" for symptom control [10], and excessive use of inhaled β2-agonists has been linked to asthma mortality [11]. It is probable that whilst β-agonists may control the acute inflammatory response, they do not have an effect on the chronic inflammatory component of asthma [9]. Indeed, the protective effect of β2-agonists against acute inflammation appears to desensitize after regular therapy [12]. This suggests that anti-inflammatory treatments should always be administered when β-agonists are used regularly or excessively. For long-acting inhaled β2-agonists it was suggested that there may be additional anti-inflammatory effects, as evidenced by the protection against the late response to allergen and the ensuing increase in airway responsiveness [13], but this is probably explained by prolonged functional antagonism, and there is no evidence that either regular short-acting β2-agonists [14], or salmeterol [15], have any effect on airway inflammation assessed by bronchial biopsy. This suggests that long-acting inhaled β2-agonists should always be used with inhaled anti-inflammatory therapy and should be considered as an additional bronchodilator when asthma is not controlled on doses of inhaled steroids of about 1 mg daily. A combination inhaler with an inhaled steroid would be the most sensible development.

Drugs which increase cAMP

Understanding the molecular mechanism of β2-agonists has prompted a search for other drugs which increase intracellular cAMP concentrations in airway smooth muscle cells. Several receptors on airway smooth muscle, other than β-receptors, may activate adenylate cyclase via a stimulatory G-protein (Gs).

Vasoactive intestinal peptide (VIP). VIP is a potent relaxant of human bronchi in vitro [16]. However, it has no bronchodilator action in asthmatic subjects when given by inhalation [17], probably because of problems with diffusion and degradation by epithelial enzymes. When given by infusion, the cardiovascular effects (flushing, tachycardia, headache, hypotension) preclude the administration of a dose high enough to bronchodilate [18]. It is unlikely that a VIP analogue, which is resistant to enzymatic degradation, would offer any great advantage over β2-agonists already available, and it would have the disadvantage of greater cardiovascular effects.

Prostaglandins. Prostaglandin E2 (PGE2) stimulates adenylate cyclase and relaxes airways in vitro. However, PGE2 has not proved to be effective as a bronchodilator in vivo, and may even lead to constriction and coughing in asthmatics, since PGE2 also stimulates afferent nerve endings in airways [19]. There is now evidence for subtypes of PGE receptors, and it is possible that the EP-receptor on sensory nerves differs from the receptor subtype on airway smooth muscle, so that a selective agonist may be developed.

G-protein/adenylate cyclase stimulation. Receptor-mediated stimulation of adenylate cyclase involves activation of Gs, which may be stimulated irreversibly by cholera toxin. Less toxic compounds which stimulate Gs are under investigation. Forskolin directly activates the catalytic subunit of adenylate cyclase, and large increases cAMP concentration in airway smooth muscle cells, but has not proved to be effective as a bronchodilator in vivo [20]. This may be because β2-agonists are effective as bronchodilators mainly through direct coupling to maxi-K channels via Gs, rather than via a rise in cAMP that is only seen with very high concentrations of β2-agonists [3].

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 [21, 22]. The isoenzymes that are involved in relaxation of airway smooth muscle (types III and IV) make up less than 5% of the total enzyme activity [23]. Selective inhibitors of these isoenzymes, such as SK&F 94836, which inhibits type III isoenzyme, may therefore be useful as bronchodilators. Recent studies suggest that in human airway smooth
methylxanthines

Theophylline has remained an important treatment in asthma for over 50 yrs, and yet its mode of action is still unknown. It now seems unlikely that bronchodilatation plays an important role in the anti-asthma effect of theophylline, and increasingly likely that some anti-inflammatory or immunomodulatory effect is important [29]. Several molecular mechanisms have been proposed to explain the actions of theophylline, but perhaps the most likely is that it non-selectively inhibits PDE. There is little doubt that theophylline has a critical role in the management of more severe asthma and it is important that its mode of action in this condition is elucidated. In a study of theophylline withdrawal in young patients with severe asthma, there was a marked deterioration of control, despite the fact that they continued to use nebulized bronchodilators and oral and inhaled steroids [30]. The currently used "therapeutic concentration" of plasma theophylline is derived from the belief that theophylline acts as a bronchodilator, but it is likely that the other anti-asthma effects of theophylline might be achieved at lower plasma concentrations, thereby avoiding the problems of toxicity and side-effects, which currently limit the use of this drug.

The major problem with theophylline is the relatively high frequency of adverse effects, several of which are due to antagonism of adenosine receptors. The development of enprofylline (3 propylxanthine), which retains the bronchodilator and PDE inhibitory effect but is not an adenosine antagonist, was an important advance. Enprofylline is an effective bronchodilator [31] and shares other anti-asthma properties of theophylline, but is not an adenosine antagonist at therapeutic concentrations [32]. Side-effects, such as diuresis, seizure and cardiac arrhythmias, are less common than with theophylline, although headache is a problem. Although enprofylline is not being developed, because of toxicological problems, other related drugs are under development.

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Selective anticholinergics

Recently it has been established that there are several distinct subtypes of muscarinic receptor [41], with differing physiological roles in the airways [42]. Muscarinic receptors inhibiting the release of acetylcholine have been described in airway cholinergic nerves of animal and are classified as M2-receptors, which are clearly different from the receptors which mediate contraction of airway smooth muscle (M1 receptors). Nonselective antagonists, such as ipratropium bromide, will inhibit prejunctional M2-receptors and, thus, increase the amount of acetylcholine released on vagal stimulation, which may then overcome the postjunctional blockade of M1-receptors, and may therefore not be as effective against reflex bronchoconstriction. Selective M1-antagonists which block only postjunctional receptors on smooth muscle should be more effective, but have proved difficult to develop, as the binding site for acetylcholine in the muscarinic receptor is very similar for each subtype of receptor [43]. Drugs which block M2 receptors may also be useful, since M1-receptors in parasympathetic ganglia facilitate ganglionic transmission and would, therefore, exaggerate cholinergic reflexes; unfortunately, M2 blockade is responsible for the drying of secretions, so that it would be important for any such drug to be delivered by aerosol.

Drugs which increase cyclic guanosine 3' 5' monophosphate (cGMP)

Atrial natriuretic factor (ANF), when given by intravenous infusion, produces a significant bronchodilator response and protects against bronchoconstrictor challenges [33]. It is probable that the effects of ANF on airways are mediated by stimulation of particulate guanylate cyclase and subsequent generation of cGMP [34]. Nitro compounds such as isosorbide dinitrate, glyceryl trinitrate (GTN) and sodium nitroprusside are thought to activate soluble guanylate cyclase. A dose-dependent relaxant effect of various nitro compounds has been demonstrated on airway smooth muscle in a number of animal studies, and this effect appears to be mediated via stimulation of soluble guanylate cyclase and subsequent generation of cGMP [34, 35]. Intravenous GTN relaxes human tracheal smooth muscle in normal subjects undergoing cardiac surgery [36]. Sublingual GTN and isosorbide dinitrate have been reported to have a bronchodilator effect in patients with asthma [37, 38], although others have not confirmed these beneficial effects [39]. It has recently been established that the endogenous neural bronchodilator in human airways is NO [40]. These studies suggest that bronchodilators with an alternative intracellular mechanism of action to β2-agonists may be possible and further investigation is warranted, particularly with inhaled formulations in order to avoid vasodilator side-effects.

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Calcium antagonists

Contraction of airway smooth muscle and release of inflammatory mediators results from an increase in intracellular [Ca++] and subsequent activation of calmodulin. Several important advances have been made in understanding the regulation of intracellular [Ca++] and many new types of drug are under development. Drugs which block calcium entry through voltage-dependent calcium channels (VDCs), such as nifedipine, verapamil and diltiazem, have not proved effective in asthma. This suggests that Ca++ entry via VDCs is not important in human airway smooth muscle contraction. Calcium entry via receptor-operated channels (ROCs) may be more important in airway smooth muscle [44], and drugs which act on these channels are currently under development. One such drug SK&F 96365 has been found to inhibit the sustained contractile response in airway smooth muscle in vitro, by preventing refilling of the calcium stores [45].

Release of Ca++ from intracellular stores is probably the most important source of calcium for contraction of airway smooth muscle. Drugs which inhibit calcium release, such as TMB-8, may have effects in airway smooth muscle, but they lack selectivity and will probably be too toxic for clinical use. Most spasmodgens contract airway smooth muscle by stimulating phosphoinositide (PI) hydrolysis [46]. Drugs which inhibit PI turnover or effects may, therefore, be of potential use in asthma. Inositol 1, 4, 5-trisphosphate (IP3) generated by PI hydrolysis, causes release of intracellular calcium by binding to specific binding sites on the endoplasmic reticulum. Heparin is a potent competitive inhibitor of IP3, binding in airway smooth muscle [47], but is not of therapeutic use, since it does not penetrate cells. Analogues of IP3 are currently under development.

Breakdown of PI also leads to the formation of diacylglycerol, which activates protein kinase C (PKC). This enzyme regulates many cellular events, including slow contractile responses. Antagonists of PKC, such as staurosporine lack specificity, but more selective PKC inhibitors, such as Ro 31-8425, are under development. The recognition that there are several isoenzymes of PKC may make it possible to develop blockers selective to certain cell types or functions in the future [48].

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 electromorphologically and with several selective toxins and drugs [49]. Drugs which selectively activate a K+ channel in smooth muscle, such as BRL 3491 (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 [50]. 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 [51]. In vivo it has no bronchodilator effect or protective effect against bronchoconstrictor challenge at maximally tolerat ed oral doses [52], but cromakalim has been shown to offer a small protection against the fall in lung function at night in asthmatic patients [53]. 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 [54].

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 [55], 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 adenosine triphosphate (ATP)-dependent channel (which opens in response to a fall in intracellular ATP concentrations). Relaxation of airway smooth muscle in response to β-agonists and theophylline appears to involve another type of channel, a calcium-activated K+ channel which is selectively blocked by charybdotoxin and iberiotoxin [1, 2, 56]. Development of activators of this channel may, therefore, be an important target for future development.

Anti-inflammatory drugs

There are several new approaches to controlling inflammation in asthmatic airways (table 2).

Corticosteroids

Corticosteroids are the most efficacious treatment currently available for the long-term management of asthma. Steroids of high topical potency, such as beclomethasone dipropionate and budesonide, are highly effective when given by inhalation. Future advances will depend upon the development of inhaled steroids of even higher topical potency or which are metabolized locally ("hit and run" steroids), so that the local dose of steroids in the airways will be increased without the systemic effects, which currently limit the dose of steroids which are rapidly metabolized in the
Anti-inflammatory also bind to steroid receptors and that this interaction occurs with low concentrations of steroids. Such an interaction between steroids and transcription factors has recently been demonstrated in human lung [62]. In the future it may be possible to develop drugs that also bind to AP-1 or other transcription factors to prevent their interaction with target genes.

Table 2. — Anti-inflammatory agents for asthma

<table>
<thead>
<tr>
<th>Existing</th>
<th>Novel</th>
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<tbody>
<tr>
<td>Corticosteroids: increased topical effect (budesonide, fluticasone)</td>
<td>Mediator antagonists (LTD₄, 5-LO, PAF antagonists)</td>
</tr>
<tr>
<td>Cromoglycate: increased potency/effect (nedocromil, frusenide)</td>
<td>Phospholipase A²/C/D inhibitors</td>
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<td></td>
<td>Neurogenic inflammation inhibitors (µ-opioids, SP antagonists)</td>
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<tr>
<td></td>
<td>Immunomodulators (cyclosporin A, FK 506, rapamycin)</td>
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<tr>
<td></td>
<td>Cytokine inhibitors (IL-5 inhibitor)</td>
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<tr>
<td></td>
<td>iG suppressors (IL-4 inhibitors)</td>
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<tr>
<td></td>
<td>LTD₄; leukotriene D₄; 5-LO: 5-lipoxygenase; PAF; platelet-activating factors; IL: interleukin.</td>
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</table>

Because steroids are so effective in the control of asthma, an important goal of research is to identify the particular cellular and molecular mechanisms which are of critical importance in asthmatic inflammation. This may then lead in the future to non-steroidal drugs which mimic the beneficial effects, without the side-effects which are due to the other actions of steroids. The molecular basis of steroid action involves interaction with a cytosolic glucocorticosteroid receptor, which then interacts with specific nucleotide sequences on the upstream regulatory elements of certain target genes to either increase (e.g. lipocortin-1, β-adrenoceptors) or decrease (e.g. cytokines) the rate of transcription [59]. It might be possible in the future to mimic certain aspects of steroid action by developing agents which selectively influence the transcription of the same genes. In addition to effects of steroids on gene transcription, it has recently been recognized that the activated glucocorticoid receptor may interact directly with other activated transcription factors in the cell via a protein-protein interaction [60, 61]. Many cytokines activate a transcription factor called activator protein-1 (AP-1), which directly interacts with the activated steroid receptor, and that this interaction occurs with low concentrations of steroids. Such an interaction between steroids and transcription factors has recently been demonstrated in human lung [62]. In the future it may be possible to develop drugs that also bind to AP-1 or other transcription factors to prevent their interaction with target genes.

Lipocortin

Steroids stimulate the production of a protein, lipocortin-1, which inhibits phospholipase A₂ (PLA₂) [63], the enzyme which leads to the generation of arachidonic acid and platelet-activating factor (PAF). Recombinant human lipocortin-1 is now available, but there might be problems in delivering such an agent, and it may be degraded at inflammatory sites. The presumed advantage of lipocortin might be reduction in glucocorticoid side-effects. However, there are doubts as to whether many of the effects of steroids are mediated via PLA₂ inhibition [64].

Anti-allergic drugs

Sodium cromoglycate is effective in controlling mild asthma [65]. It appears to have a specific action on allergic inflammation, and yet its molecular mechanism of action remains a mystery. Although it was believed that its primary mode of action was by inhibiting mast cell mediator release, it has now been demonstrated that it has effects on several other inflammatory cells and on sensory nerves. Nedocromil sodium has a very similar profile of anti-asthma effects, but is more potent and it may be possible to maintain control with less frequent administration [66]. Both cromoglycate and nedocromil sodium must be given by inhalation and all attempts to develop orally active drugs of this type have been unsuccessful, possibly because topical administration is critical to their efficacy.

Mediator antagonists

Many different inflammatory mediators have now been implicated in asthma [67], and several specific receptor antagonists and synthesis inhibitors have been developed, which will prove invaluable in working out the contribution of each mediator. As many mediators probably contribute to the pathological features of asthma, it seems unlikely that a single antagonist will have a major clinical effect, compared with nonspecific agents such as β-agonists and corticosteroids. However, until such drugs have been evaluated in careful clinical studies, it is not possible to predict their value.

Lipid mediators may play an important role in asthmatic inflammation. Several potent leukotriene, PAF and thromboxane antagonists have now been developed and are currently undergoing clinical trials in asthma [68]. Initial results appear to suggest that potent leukotriene antagonists, such as MK-571 and ICI 204, 219, have a significant protective effect against some constrictor challenges, such as exercise and allergen [69, 70], and long-term clinical trials are now underway, with encouraging preliminary results [71].

Although PAF has several properties which suggest that it may play an important role in asthma [72], recent studies with potent PAF antagonists show no effect on allergen challenge [73–75]. The most
potent PAF antagonist currently available is UK 74,505, which after a single oral dose inhibits the airway effects of inhaled PAF for up to 24 h [76], and yet is ineffective in allergen challenge [77], indicating that such drugs will probably have no place in the future management of asthma.

Bradykinin has also attracted attention as a potential mediator of asthma symptoms, since bradykinin appears to be the inflammatory mediator produced in asthma that is most likely to activate sensory nerves in the airway [78]. A potent and stable bradykinin BK_2-receptor antagonist HOE 140 has recently been developed [79] and may have therapeutic potential as a modulator of asthma symptoms.

It seems rather unlikely that antagonizing a single mediator will ever be as useful as less specific therapies, but such therapies may have the advantage of fewer side-effects and oral administration. Certain types of asthmatic patient may respond much better to these more specific therapies. For example, it seems likely that aspirin-sensitive asthmatic patients may particularly benefit from leukotriene D_4 (LTD_4)-antagonists [80].

Enzyme inhibitors

An alternative to antagonists of mediator receptors are drugs which inhibit the enzymes involved in mediator synthesis. Since PLA_2 appears to be of critical importance in the generation of all lipid mediators, it is a suitable target for inhibitory drugs. Drugs other than steroids which inhibit PLA_2, such as mepacrine, might be expected to share the beneficial effects of steroids, but this drug is weak and nonspecific. More potent PLA_2 inhibitors, such as manoolide, derived from a sponge, are also nonselective [81]. It is now clear that there may be many forms of PLA_2, and a high molecular weight cytosolic PLA_2 that is arachidonic acid-selective has recently been cloned [82]. This may make it more feasible to select inhibitors by random screening, but whether PLA_2-inhibitors would offer any advantage over 5-lipoxygenase inhibitors is uncertain, in the light of the fact that neither cyclo-oxygenase inhibitors nor PAF receptor antagonists are effective in asthma. Inhibition of phospholipase C, which is the enzyme leading to PI breakdown, could also be useful, as discussed above. Phospholipase D (PLD) appears to play a critical role in the priming of inflammatory cells and, therefore, may be an important target in asthma [83]. Although poor inhibitors such as wortmannin are available, more selective PLD inhibitors are under development.

Cyclo-oxygenase inhibitors, which inhibit the formation of prostaglandins and thromboxane, are of no obvious therapeutic value in asthma [84, 85], and in the small group of asthmatics with aspirin-sensitive asthma they may cause a deterioration.

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 small inhibitory effect on allergen-induced responses and leukotriene production [86], although more encouraging results have been obtained in cold air challenge [87]. Zileuton, like 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 apparently binds to a 5-LO activating protein (FLAP) in the cell membrane, to which cytosolic 5-LO must bind in order to be active [88]. There is a theoretical advantage to the use of 5-LO inhibitors, compared with leukotriene antagonists, since the formation of leukotriene B_4 (LTB_4) and other 5-LO products, as well as sulphidopeptide 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 [89]. There are several approaches to inhibiting these local reflexes [90]. Antagonists of sensory neuropeptides, such as substance P, neurokinin A and calcitonin gene-related peptide, are currently under development. Most of the inflammatory effects of tachykinins are mediated by neurokinin-1 (NK_1)-receptors and several selective antagonists have been developed [91]. A potent nonpeptide NK_1-antagonist, CP-96, 345, has recently been described, which may prove to be a very useful lead compound, which avoids all the problems associated with the development of peptide antagonists [92]. This antagonist is extremely effective in blocking the inflammatory effects of tachykinins released endogenously by nerve stimulation [93].

Another approach is to inhibit the release of these peptides from C-fibres rather 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 [90]. Opioids which act peripherally, such as the opioid peptide BW 443C, may be effective in reducing neurogenic inflammation in asthma (and also the associated sensory symptoms such as cough) [94]. Inhaled BW 443C has no effect on resting lung function or on bronchoconstriction induced by metabisulphite [95], although this peptide is likely to be rapidly degraded by epithelial enzymes. More stable, peripherally active, opioid agonists are now under development. Several other agonists act on pre-junctional receptors on sensory nerves in airways to inhibit neuropeptide release; these include α_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 [96].
The surface enzyme, neutral endopeptidase (NEP), is important in degrading several peptides with bronchoconstrictor and inflammatory effects in the airways, including tachykinins, bradykinin and endothelins. There is circumstantial evidence from animal studies that it may be deficient in asthmatic airways [97]. Recombinant human NEP is capable of reversing any induced deficiency of the enzyme and, therefore, has some potential in asthma, although delivery is a problem, as it is a relatively large protein.

Another possibility is to inhibit activation of sensory nerves. This may be achieved by drugs such as sodium cromoglycate and nedocromil sodium, which appear to stabilize unmyelinated nerves in asthmatics [98]. Another drug which has a similar profile of activity is the loop diuretic frusemide.

A more radical solution is to deplete sensory nerves of neuropeptides using capsaicin. This approach has been successful in vasomotor rhinitis and local application of capsaicin markedly reduces symptoms of rhinitis for several months [99].

**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 prostaglandin F₂α (PGF₂α) [100-102]. These effects mimic those of sodium cromoglycate but, in addition, inhaled frusemide inhibits certain types of induced cough [103]. 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⁻ co-transporter in renal tubular cells, but the more potent inhibitor bumetanide is ineffective in the same challenges [104]. Some effects of frusemide are mediated by the release of PGE₂, 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. Indeed frusemide is effective in blocking eosinophil activation and airway sensory nerves, and its actions are mimicked by Cl⁻ channel blocking drugs [105]. Frusemide itself causes diuresis when inhaled in high concentrations, but it is possible that derivatives with less diuretic potency or that selective Cl⁻ channel blockers may, in the future be developed for use in asthma.

**Cytokine inhibitors**

There is increasing evidence that cytokines may participate in the inflammatory response in asthma. Interleukin (IL)-1, IL-8 tumour necrosis factor and granulocyte-macrophage colony-stimulating factor (GM-CSF) from macrophages, and IL-3, IL-4 and IL-5 from CD4⁺ T-lymphocytes may all be involved in the chronic inflammation in asthmatic airways, together with additional cytokines (GM-CSF, IL-6, IL-8), which may be released from epithelial cells of the airways. Drugs which interfere with the production or action of these cytokines may, therefore, prove to be of benefit in asthma. Indeed, corticosteroids may be effective in asthma by suppressing cytokine synthesis in inflammatory cells [113]. It may prove difficult to develop specific receptor antagonists for cytokines, since they are large peptides and have a very high affinity for their receptors. Strategies such as antisense nucleotides, which would inactivate the specific messenger ribonucleic acid (mRNA) encoded by cytokine genes, may be a more optimistic approach [114]. A naturally occurring antagonist of IL-1 has been isolated [115], and in experimental allergic inflammation of the airways IL-1 receptor antagonist has some inhibitory effect [116]. Studies of human recombinant IL-1ra in asthma are currently underway. Similar antagonists of other cytokines may be discovered which could lead to the development of future antagonists. Specific antibodies to various cytokines have now been developed, but while these may be suitable for revealing the roles of various cytokines [117], they would not be suitable for chronic administration. An antibody to IL-5 is effective in controlling eosinophilic inflammation after allergen in guinea-pigs [118], suggesting that IL-5 antagonism may be a promising target for more specific therapy.
Cell adhesion blockers

It is now recognized that the infiltration of inflammatory cells into tissues is dependent on adhesion of blood-borne inflammatory cells to endothelial cells prior to migration to the inflammatory site [119]. This depends upon specific glycoprotein adhesion molecules on leucocytes and on endothelial cells, which may be upregulated, or expressed on the cell surface, in response to various stimuli, such as cytokines, or mediators, such as PAF, or leukotrienes. Monoclonal antibodies which inhibit these adhesion molecules, therefore may prevent inflammatory cell infiltration. Thus, a monoclonal antibody to intercellular adhesion molecule-1 (ICAM-1) on endothelial cells prevents eosinophil infiltration into airways and increase in bronchial reactivity after allergen exposure in sensitized primates [120]. Synthetic peptides, with the sequence which is critical for adhesion, may have therapeutic potential. Thus, some integrins bind to a tripeptide sequence Arg-Gly-Asp (RGD), which may therefore inhibit leukocyte adhesion. Another possibility is to inhibit the expression of adhesion molecules on the cell surface. For example, 3-deazaadenosine inhibits cytokine-mediated induction of ICAM-1 [121]. Whilst inhibition of adhesion molecules is an attractive new approach to the treatment of inflammatory disease, there may be potential dangers in inhibiting immune responses, leading to increased infections and increased risks of neoplasia. If some selectivity of effect could be achieved then this would be of less concern. Adhesion of eosinophils appears to involve an interaction between vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells and very late activation antigen-4 (VLA4) on eosinophils [122], either of which may be a more specific target than ICAM-1.

Immunoglobulin E (IgE) suppression

Since release of mediators in asthma may be IgE-dependent, an alternative approach may be to inhibit the synthesis of IgE. Suppressor factors which inhibit IgE synthesis, and which are related in structure to the IgE receptor, have been described, but have proved disappointing in vivo. IgE synthesis by B-lymphocytes is dependent on IL-4, so that IL-4 synthesis inhibitors or receptor antagonists would be useful in allergy suppression [123].

Immunotherapy

Although immunotherapy, as currently practised, has been disappointing in the therapy of asthma, it is likely that more effective vaccines will be developed in the future. As the complex mechanisms of antigen presentation and the interaction between antigen-presenting cells and T-lymphocyte receptors are elucidated this may lead to the development of peptides which will block allergen-induced immune reactions [124, 125].

Conclusions

Many different therapeutic approaches to the treatment of asthma may be possible, yet there have been few new drugs which have reached the clinic. \( \beta_2 \)-agonists are by far the most effective bronchodilator drugs and lead to rapid symptomatic relief. Now that inhaled \( \beta_2 \)-agonists with a long duration of action have been developed, it is difficult to imagine that more effective bronchodilators could be discovered. Similarly, inhaled corticosteroids are extremely effective as chronic treatment in asthma and suppress the underlying inflammatory process. For most patients, a short-acting \( \beta \)-agonist on demand and regular inhaled steroids are sufficient to give excellent control of asthma [126]. For some patients, a fixed combination \( \beta \)-agonist and steroid inhaler may be a useful development, since they will improve the compliance of inhaled steroids (which is poor because of the lack of immediate bronchodilator effect). The ideal drug for asthma would probably be a tablet which can be administered once daily to improve compliance. It should have no side-effects and this means that it should be specific for the abnormality of asthma (or allergy).

Future developments in asthma therapy should be directed towards the inflammatory mechanisms and perhaps more specific therapy may one day be developed. The possibility of developing a "cure" for asthma seems remote, but when more is known about the genetic abnormalities of asthma it may be possible to search for such a therapy. Advances in molecular biology may aid the development of drugs which can specifically switch off relevant genes, but more must be discovered about the basic mechanisms of asthma before such advances are possible.

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