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Drug therapy in asthma bronchiale in the new millennium

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Asthma bronchiale represents a major health issue in industrialized countries and will likely remain so for decades. The drug treatment of asthma demonstrates certain peculiarities: revolutionary new drug introductions happen almost each quarter century. With improved understanding of asthma pathogenesis and drug metabolism, the potential for specific targeted and constructed therapies has become evident. Monoclonal antibodies to IgE and certain cytokines such IL-4 and IL-5 are being investigated as possible treatments for asthma. Similarly, preliminary studies of selective phosphodiesterase inhibitors in asthmatic patients have been encouraging. Other potential therapies include for example inhibitors of cytokine synthesis, promoters of Th2-Th1 switch, adenosine receptor agonists or antagonists, etc.. A new way is represented by a modified retrometabolic drug design resulting in so-called soft drugs. The first representative of this new drug class is loteprednol etabote (LE), a non-fluorinated glucocorticoid approved for the allergic ophthalmological indications and now in clinical trial for the treatment of allergic airway diseases. Today's intensive search for new treatments should ensure a greater diversity of therapeutic possibilities for the management of asthma in the new millennium.

1. Introduction

Bronchial asthma affects ca. 5% of adults and about 10% of children worldwide. It represents a major health issue in industrialized countries and will likely remain so for decades. Its pathophysiology is multifactorial and complex. Heredity, environmental risks, occupational exposure relate to it. Asthma bronchiale is predominantly a small airways disease whose features include bronchoconstriction and airway inflammation which is characterized by the presence of eosinophil granulocytes. The continuous increase in prevalence, severity, and mortality in industrialized countries highlights the deficiency of suitable treatment. Neither doctors nor patients are completely satisfied with the effects options of the several drugs currently available. There is no doubt that we urgently need new and effective drugs which are able to treat or even possibly cure the allergic inflammation.

The drug treatment of asthma demonstrates certain peculiarities: revolutionary new drug introductions happen almost each quarter century. The first step in this direction was the introduction of theophylline followed by β_2-adrenoceptor agonists, corticosteroids and disodium cromoglycate. The drug therapy of the last decader was characterized by the introduction of the long-acting β_2-adrenoceptor agonists, leukotrine receptor antagonists, and by some steroids with lower side-effect inducing potential. Recent guidelines emphasize the important role of inflammation and recommend the early institution of anti-inflammatory treatment. However, many patients remain undertreated because there is a general phobia about corticosteroids. With improved understanding of asthma pathogenesis and drug metabolism, the potential for specific targeted and constructed therapies has become evident.

2. Targets outside the cellular membrane

The first targets are outside the cellular membrane, especially IgE and certain cytokines such as IL-4 and IL-5. IgE has a critical role in the pathogenesis of allergic asthma. In murine asthma models, it has clearly been demonstrated that anti-IgE monoclonal antibody (mAb) depletes IgE and significantly reduces lung eosinophilic inflammation [1]. The humanized murine monoclonal antibody to IgE, rhu-mAb-E25 recognizes the specific Fcε3 portion of circulating IgE that binds to the high-affine IgE-receptor. In clinical studies, administration of rhu-mAb-E25 resulted not only in reduction of IgE-concentration but also in reduction of corticosteroid need, decreased asthma exacerbations [2]. IL-5 is the predominant cytokine associated with antigen-induced eosinophil inflammation in the airways. Humanized anti-IL-5 mAbs are currently in clinical testing [3]. Asthma is characterized by locally increased levels of IL-4, a Th2-cell typical cytokine. Blockade of IL-4 receptor (R) with anti-IL-4R significantly reduces antigen-induced airway hyperresponsiveness and pulmonary eosinophilia in mice [4].

3. Targets at the membrane

Possible targets localized at or in the outside membrane are summarized in Table 1. Since the discovery of the first

Table 1: Targets at the membrane

Receptor agonists/antagonists

- Selective histamine H_1 receptor antagonists
- Muscarinergic (M_3) receptor antagonists
- Selective β_2-adrenoceptor agonists
- Cysteinyl-leukotriene antagonists
- LTB_4 antagonists
- Bradykinin BK_2 receptor antagonists
- Adenosine A_{2B} receptor antagonists
- Adenosine A_3 receptor agonists
- IL-4 or IL-5 receptor antagonists
- IL-10-receptor agonists
- Blocking compounds at the common β_c chain of IL-3, IL-5 and GM-CSF-receptor
- etc.

Openers or blockers of channels

- Potassium channel openers
- Chloride channel blockers (e.g. cromones, furosemide)

antihistamines, the question always arises: Do antihistamines have a role in asthma therapy? Antihistamines of the first generation were obsolete not only due to their strong sedative effect but also due to the definite lack of any therapeutically relevant effects. Second generation of antihistamines such as azelastine, cetirizine, fexofenadine, loratadine, etc. have moderate effect in attenuating asthmatic bronchospam but they have certain anti-inflammatory activity. They are not recommended as a single agent for treating bronchial asthma. However, modern antihistamines can be useful first of all in patients suffering from rhinitis in coexistence with asthma. Selective β_2-adrenoceptor agonists belong to the standard therapy of asthma bronchiale. Since short- and long-term acting compounds are present, a revolutionary development on this special field of antiasthmatics is not anticipated. Stronger bronchodilatory drugs than β_2-adrenoceptor agonists are not known until now and it is very unlikely that such will be discovered in the near future (see also Table 2). Antimuscarinic treatment for asthma goes back, since they do not offer any advantage over β_2-adrenoceptor agonists. However, the use of anticholinergics in chronic obstructive pulmonary disease (COPD) and allergic rhinitis will enormously increase [5]. The role of leukotriene receptor antagonists in the treatment of asthma is in evolution. Although there is a considerably heterogeneity with good and poor responders, LT-receptor antagonists will have their place in asthma management [6, 7]. It seems likely that aspirine-sensitive patients may be benefit from by LT-antagonists. In animal studies it has been demonstrated that LTB_4 may participate in antigen-induced bronchial hyperresponsiveness but not in eosinophil infiltration [8]. The role of LTB4 in the pathogenesis of asthma is still contradictorily discussed. It is very likely that LTB_4 plays a more important role in COPD than in asthma. Plasma kinins are involved in a variety of pathophysiological conditions. As a consequence of the progress in the area of kinin receptors, specific kinin receptor antagonists will be available soon. To our present knowledge, blockade of NK2-receptor may alter acute airway responses to antigen in animals but not antigen-induced lung eosinophilia [9]. Adenosine is an endogenous nucleoside that is released under several pathological conditions. Its receptors are widely distributed in the body. Furthermore, there is a relatively complicated species dependency in sensitivity of adenosine receptors. Based on our present knowledge, it is likely that adenosine A_{2B}-antagonists and A_3-agonists will be of interest in the future asthma therapy [10]. First selective and highly potent adenosine ligands are now under development. According to recent results, a murine IL-4 mutant protein receptor antagonist inhibited the development of airway eosinophilia and bronchial hyperresponsiveness in actively sensitized mice [7].

The outer cell membrane also contains ion channels which can also be suitable targets for drug development. First of all, potassium and chloride channels can be considered as possible interesting therapeutic targets. The role of K_{ATP} channel openers for the treatment of airway hyperreactivity has recently been summarized by Buchheit and Fozard [11]. Earlier studies with cromolyn and nedocromil have focused the interest on chloride channels: These agents have been shown to block Cl^- currents [12]. It has recently been shown that gob-5, a member of the calcium-activated chloride channel family, is a key molecule in the induction of murine asthma [13]. Therefore, it is likely that compounds blocking Cl^--channels may have certain benefit in the future asthma therapy.

4. Targets in the cytosol

In the cell cytosol, there are also some possible targets (Table 2). Stimulators of adenylate or guanylate cyclase such as forskolin and urodilatin are definitely too weak bronchodilators in order to replace β_2-adrenoceptor agonists. Nevertheless, they could be novel partners for classical bronchodilatoy drugs since they can further improve lung function in combination with established β_2-adrenoceptor agonists [14]. All other cytosolic targets are more or less related to inflammation. Over recent years it has become widely accepted that asthma is a chronic persistent inflammatory condition. Therefore, all new targets involved in the regulation of inflammatory cells and mediators may be of future interest. Inhibitors of 5-lipoxygenase

Table 2: Targets in the cytosol

- Stimulators of adenylate or guanylate cyclase
  e.g. forskolin, ANP, urodilatin
- Inhibitors of phosphodiesterase 4
  e.g. rolipram, roflumilast, AWD 12–281
- Inhibitors of phosphodiesterase 7
  e.g. not known at present
- Inhibitors of FLAP (5-lipoxygease activating protein)
  e.g. MK 886, Bay × 1005
- Inhibitors of 5-lipoxygenase
  e.g. zileuton
- Tryptase inhibitors
  e.g. APC 366, AMG-126737
- Inhibitiors of iNOS
  e.g. 1400W

Table 3: PDE isoenzyme profiles in human inflammatory/immunocompetent cells

Cell-type	PDE1	PDE2	PDE3	PDE4	PDE5	PDE6	PDE7	PDE8	PDE9
Mast cells	×			×	×				
Basophils			×	×					
Eosinophils				×					
Neutrophils				×					
Monocytes				×					
Macrophages	×	×	×	×					
B-lymphocytes				×			×		
T-lymphocytes		×	×	×			×[1]		
Platelets		×	×		×				
Endothelial cells		×		×	×				
Epithelial cells	×	×	×	×	×		×	×	
Smooth muscle cells		×	×	×					

[1] only expressed

such as zileuton and inhibitors of FLAP (5-lipoxygenase activating protein) are already used in asthma treatment [15].

At least 11 families of distinct phosphodiesterase (PDE) isoenzymes are known to regulate the function of many cells. It is of interest that inflammatory cells involved in asthma pathogenesis preferentially express PDE4. Therefore it was self-evident to search for highly selective inhibitors of this isoenzyme. Unfortunately, PDE4 inhibitors of the first generation tended to be associated with undesired effects such as headache, nausea and vomit [16]. Recently, attempts have been made to synthesize isoenzyme subtype specific inhibitors with improved the side effect profile. One of the most promising candidate is roflumilast. Both preclinical and first clinical results indicate that roflumilast could be useful in the treatment of asthma and COPD [17, 18]. Based on the unique localization of PDE7, this isoenzyme might also be an interesting target in future. However, it has to be taken into consideration that PDE7 may have a co-localization with PDE4 in the brain suggesting its involvement certain side effects such as depression, emesis [19]. First inhibitors of this isoenzyme have very recently been synthesized [20].

Human lung tryptase, a homotetrameric serine proteinase unique to mast cell secretory granules, has been implicated as a therapeutic target for asthma. AMG-126737 with a K_i-value of 90 nM inhibited the development of bronchial hyperresponsiveness in the guinea pig model of asthma [21]. Further candidates are now under clinical development.

Nitric oxide may play an important role in regulating airway function and in the pathogenesis of inflammatory lung diseases. It is likely that selective inhibitors of iNOS may be useful in asthma [22]. However, recent results indicate that iNOS-derived NO may have both beneficial and detrimental effects on allergen-induced pulmonary changes [23]. In a recent study, Koarai et al. [24] that 1400W, a selective iNOS inhibitor significantly attenuated both airway hyperresponsiveness and eosinophil accumulation in an allergic mice model.

5. Targets in the cell nucleus

The cell nucleus offers certain future targets. At present, corticosteroids are the most effective therapy to control airway inflammation. After binding to the glucocorticoid receptor, they repress the synthesis of pro-inflammatory cytokines by inhibition of the transcription factors AP-1 and NF-κB (trans-repression) (but also suppression of osteocalcin gene resulting in osteoporosis) and can also induce gene transcription (trans-activation) (e.g. increase in number of β2-adrenoceptors, increase in intraocular pressure).

Glucocorticoids are the gold standard treatment in asthma affecting most of the components involved in its pathogenesis. Not only the asthma prevalence has risen substantially in recent decades but it is an increasing cause of disability, first of all, for children. Glucocorticoids are often underdosed or underused because patients are afraid of possible unwanted effects such as growth retardation, increase of ocular pressure, cataract, osteoporosis, disturbances in glucose metabolism, etc. Some years ago, it was stated that novel inhaled steroid could be developed by reduction of absorption rate from the lung (sustained release), biotransformation by the lung or by synthesizing compounds with higher or selective tissue affinity. Bodor introduced a new group of compounds, the so-called soft steroids which have been synthesized by using the retrometabolic design [25, 26]. Recently, we have demonstrated that the soft steroid loteprednol etabonate (LE) effectively attenuate early and late phase allergic responses in animal models of asthma [27]. LE did not influence the thymus development [27]. We also investigated the changes in plasma cortisol levels in domestic pigs following high intranasal or intrapulmonary doses of LE. LE did not influence the plasma cortisol level in this steroid-sensitive species [27]. To gain more information about the mode of action, we have now investigated the effect of LE on MCP-1 (monocyte chemotactic protein) release from human epithelial A549 cells.

Chemokines play an important role in attracting cells mediating inflammatory actions in asthma disease. Recently it has been reported that epithelial cells are also a source of chemokines. We stimulated A549 cells, a lung epithelial cell line, with proinflammatory cytokines IL-1β and TNF-alpha and studied the induction of different CC-chemokines by real-time RT-PCR and ELISA. IL-8, RANTES and MCP-1 were found to be rapidly upregulated after stimulation. The addition of loteprednol prior to stimulation led to a dose dependent reduction of chemokine release.

The glucocorticoid receptor gene may be an interesting candidate for gene therapy in certain population of asthmatic patients. Since qualitative and quantitative defects of glucocorticoid receptors have been reported in corticoresistant patients, it is likely that these patients may have benefit from such a gene therapy [28].

In most cells trans-activating NF-κB induces many inflammatory proteins as well as its own inhibitor, IκBα, thus assuring a transient response upon stimulation. However, NF-κB-dependent inflammatory gene expression is persistent in asthmatic bronchi, even after allergen elimination [29]. An interesting future approach could be the direct inhibition of NF-κB by a new compound [30]. Very recently, Das et al. [31] have shown that inhibition of NF-κB activity prevented the expression of transcription factor GATA-3 which plays a critical role in Th2 differentiation and allergic inflammation indicating a probably pivotal role of NF-κB again.

6. Targets of signal transduction pathways

Concerning signal transduction, there are also several possibilities to find new targets suitable for asthma therapy. STAT6 (signal transducer and activator of transcription factor) is a transcription factor essential for Th2 cell differentiation. It also controls Th2 recruitment and effector function in allergic inflammation. Mathew et al. [32] found that all of the features of asthma were absent in STAT6(−/−)-mice. Therefore, the interruption of STAT6 signaling in resident cells of the lung could be a promising new approach to asthma therapy. Another interesting possibility is the inhibition of tyrosine kinase [30]. Leflunomide, a novel immunomodulatory drug, has two biochemical activities: inhibition of tyrosine phosphorylation and inhibition of pyrimidine nucleotide synthesis [33]. However, its effect on tyrosine kinases has recently been questioned [34].

There are several new compounds whose mode of action is not clearly defined. One of them is heparin, a glycosaminoglycan released exclusively from mast cells, is believed to possess anti-inflammatory actions. In fact, heparin inhibits allergen-induced eosinophil recruitment in the guinea pig lung via a mechanism unrelated to its anticoagulant activity [35].

Today's intensive search for new treatments should ensure a greater diversity of therapeutic possibilities for the management of asthma in the next millennium. Novel treatment modalities described above will hopefully permit a more selective and effective suppression of airways inflammation and bronchospasm in asthmatics with less side-effect inducing capability.

Acknowledgements: The authors thank their colleagues Sabine Heer, BSc, Hildegard Kuss, PhD, Matthias Fiedler, BSc, Degenhard Marx, DVM for their valuable contributions to this paper.

This research paper was presented during the 3rd Conference on Retrometabolism Based Drug Design and Targeting, May 13–16, 2001, Amelia Island. Florida, USA

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