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Can corticosteroids be beaten in future asthma therapy?

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Received August 8, 2005, accepted September 6, 2005

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Pharmazie 61: 122–124 (2006)

Despite the enormous therapeutic advance, there is a general trend towards increasing morbidity and mortality due to asthma, which suggests that there is a need for new and improved treatments. The past decade was determined by the so-called "new biology" that identified and cloned almost all receptors and ion channels. This scientific revolution should lead to a more rapid identification of novel targets for major diseases and processes like high throughput screening and combinatorial chemistry should have improved and fastened the development of new drugs. Interestingly, exactly the opposite has happened. With the exception of leukotriene receptor antagonists and some monoclonal antibodies, no new developments have been introduced into asthma therapy during the last decade. The most promising approach is still to find drugs like corticosteroids with multiple functions. However, there is no evidence at the very moment that corticosteroids can be beaten in the next ten years. Therefore, our task is to improve the corticosteroids and make therapy with them even safer. The so-called soft-steroids such as loteprednol and etiprednol belong to the future promising therapeutically effective and safe treatments of allergic disorders.

1. Introduction

Despite enormous therapeutic advances, bronchial asthma, one of the most common chronic inflammatory diseases of our hemisphere, remains a highly prevalent and serious health problem. Asthma is a disease that affects about 5% of all adults worldwide. In children, the number is even twice as high, which is also due to the high percentage of allergic asthmatics (Maziak et al. 2003). Its pathophysiology is multifactorial and complex, characterized by variable airway obstruction, bronchial hyperresponsiveness and – as a core feature – airway inflammation with infiltrating eosinophils, activated lymphocytes as well as mast cells.

The pillars of asthma therapy are the $ß_2$-adrenergic agonists along with glucocorticoids – often and appropriately used in combination. Other therapeutical approaches comprise anticholinergics, chromones, theophylline, antileukotriens and omalizumab, with the latter two being the only novel drug classes that have been put on the market during the last three decades. However, further studies will show if an anti-IgE therapy has an advantageous risk-benefit ratio. Among all asthma drugs, corticosteroids are in fact the only therapeutic approach that can effectively suppress the inflammation predominant in asthma.

As both asthma prevalence and mortality have increased dramatically over the past decades and as occupational asthma is predicted to be the pre-eminent occupational lung disease in the next decade, there is no doubt that we have an urgent need for new strategies in our fight against this disease. The so-called single mediator approach, one strategy developed and pursued during the last several years, appears to be ineffective in the treatment of asthma. Drugs with multiple modes of action and various targets – in fact the way corticosteroids exert their effects – seem to be more effective. Thus, the present drug screening strategies should be reconsidered and be replaced by novel and more serendipity-based research.

2. Asthma drug development in the last decade

During the past decade, the so-called "new biology" identified and cloned almost all receptors and ion channels. Its major goal was to accelerate the identification of possible novel targets for major diseases. As a consequence, a wide array of targets have emerged that control cell influx and activation, inflammatory mediator release and activity, as well as tissue proliferation and degradation.

Together with high throughput screening technologies and combinatorial chemistry, the pharmaceutical industry thought to have ideal tools for both revolutionary high-speed drug discovery and development. However, these hopes and wishes have not been fulfilled. We are still waiting for new and effective drugs in the fight against asthma. Since many other diseases can meanwhile be combated adequately, we must ask ourselves what was wrong in the past asthma drug research.

3. The single mediator approach

Monotherapy, the use of a single drug to treat asthma, has been and remains relatively common. This is based on the belief that the great preponderance of pathologies and symptoms of asthma can be explained by the actions of

just one of several mediators of the disease. This is a tempting idea which has unfortunately not been fulfilled.
One example for the single mediator approach is histamine, which certainly belongs to the key mediators in allergic diseases and which was identified in the beginning of the last century. With the H_1-receptor antagonists, effective treatment of seasonal and perennial allergic rhinitis as well as urticaria and angioedema was soon possible. But their role in asthma therapy was controversial. Today they are obsolete not only due to their strong sedative side effects but also due to their definite lack of any therapeutically relevant effects. With the development of the second-generation non-sedating H_1-histamine receptor antagonists in the 1980s, the debate was revived. Today it is widely accepted that the new generation antihistamines have only moderate effects in attenuating asthmatic bronchospasm, but we have to admit that they do have certain anti-inflammatory activity (Busse et al. 1996). Nevertheless, the therapeutic usefulness of antihistamines of the second generation still remains more than questionable (Larsen 2001).
Another interesting example is represented by IL-4. There is no doubt that it is – together with IL-13 – the key cytokine in the development of Th2 cell responses and it apparently plays a critical role in asthma. However, until now at least all monotherapeutic anti-IL-4 strategies have remained without success (Ichinose and Barnes 2004).
On the other hand, a good example that a single "mediator" can probably lead to a successful anti-asthmatic therapy is the target phosphodiesterase (PDE) type 4 isoenzyme. It catalyzes the breakdown of cyclic AMP to the respective 5′-nucleotide monophosphate. Blocking this enzyme leads to an increase in cAMP, and as a result in a variety of anti-inflammatory actions. Therefore, PDE4 inhibitors can be seen as affecting a single mediator, with, however, exerting multiple effects on airway inflammation (Baeumer et al. 2005).
As asthma itself can be seen as a "dirty" disease with the involvement of several mediators, it needs "dirty" targets or drugs with various modes of action in different directions.

4. Improved corticosteroids

Corticosteroids can be regarded as multiple "cure-alls": Not only are they able to attenuate the inflammatory sides of the disease, but they are also capable of amplifying many anti-inflammatory pathways. They exert their effects in many directions, and this is what makes them unique and indispensable in the therapy of various other inflammatory diseases apart from asthma. Understanding the "ambiguous" molecular mechanisms of corticosteroids may on the one hand help us to design improved and novel corticosteroids with less systemic side effects, on the other hand it might be indispensable for the development of revolutionary approaches to other anti-inflammatory drugs. One step in the direction of novel glucocorticoids was made with the development of the so-called soft steroids as for example loteprednol or etiprednol (Szelenyi et al. 2000; Kurucz et al. 2003). The principle applied here is called "retrometabolic drug design" and has been applied successfully in many other areas of drug design before (Bodor 1995, 2001). With regard to asthma, these drugs are active at the site of action, for example after inhalation into the lungs, but are inactivated very quickly – if possible in a one-step metabolic reaction – when absorbed systemically. Furthermore, they seem to have the ability to dissociate transrepressing, i.e. the desired anti-inflammatory effects, and transactivating properties, the undesired side effects as for example on gluconeogenesis and arterial and ocular tension. The dissociation of different glucocorticoid effects and the concentration on transrepressional activities many help us to minimize unwanted side effects.
Apart from novel glucocorticoids, we are in desperate need for potent alternatives with different modes of action, not only to improve regular, guideline-related asthma therapy, but for instance in the treatment of corticosteroid-resistant patients or other inflammatory airway diseases like COPD where corticosteroids seem to be not very effective. Therefore, we have to look at the disease as a whole, to better understand the molecular mechanisms of asthma and to concentrate not only on single mediators but on cellular targets with multiple functions.
In the following we point out some interesting examples for the multiple target hypothesis, demonstrate their possible effects in asthma and indicate their possibilities as alternative treatments in the near future.

5. Multidirectional drugs

Experimental evidence suggests a possible pivotal role for the nuclear factor-κB (NF-κB) both at the stage of initiation and perpetuation of chronic inflammation. Although there is no NF-κB antagonist under promising clinical development to our knowledge, based on its multifaceted role in inflammation, NF-κB may nevertheless represent an interesting future target for asthma therapy.
Peroxisome proliferator-activated receptor-γ (PPAR-γ) has been shown to be of importance in the control of inflammatory responses, including inflammatory lung diseases, as it acts on various types of cells. PPAR-γ ligands might possibly have new therapeutic potential for airway inflammation in asthma (Honda et al. 2004).
A key signaling cascade in many cellular processes including inflammation is the mitogen-activated protein kinase (MAPK) pathway. MAPKs are serine/threonine kinases and are divided into the extracellular signal-regulated kinase ERK-1/2, the c-Jun N-terminal kinase (JNK) and the p38 MAP kinase. As protein phosphorylation plays an important role in many cell functions including inflammatory processes, these pathways can serve as possible targets themselves or targets upstream or downstream the cascade can be of relevance in the treatment of asthma. There is experimental evidence that, similarly to JNK, ERK-1/2 controls the release of allergic mediators and both are responsible for the induction of pro-inflammatory cytokines in mast cells, and, therefore, they might serve as possible targets (Chialda et al. 2005).
Nucleic acid-based methods use antisense oligonucleotides (ODNs) inhaled and deposited into the airways to specifically modulate receptors of inflammatory mediators. For the treatment of asthma, pulmonary administration of antisense oligonucleotides (ODNs) is specially favorable. The expectation with respirable antisense oligodesoxynucleotides (RASONs) directed against the adenosine A_1 receptor was great, the success insignificant. The reason of this apparent disappointment might be sought in the lack of A1 adenosine receptors in the human lung. Antisense ODNs against various transcription factors relevant for the induction of Th2 cells have been evaluated, but we are still waiting for the therapeutic acceptance. Therefore, the question is legitimate whether this approach should be followed further or if it is more advisable to turn to new strategies.

6. Outlook

Doubtless, there is still an enormous requirement for new treatments of asthma. We have learnt during the last several years that corticosteroids are the most successful remedies in asthma therapy. We have also learnt that the way to success is apparently long and tricky. Therefore, it is hazardous to speculate that we will soon have novel revolutionary therapies for asthma. The ideal approach here might be to use targets upstream or downstream of pathways and furthermore to apply the respective drugs topically and thus avoid side effects. Meanwhile, and with the introduction of loteprednol, there is the legitimate hope that this class of drugs will find their appropriate position in the future asthma therapy.

This research paper was presented during the 5th Conference on Retrometabolism Based Drug Design and Targeting. May 8–11, 2005, Hakone, Japan.

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