Acta Bio Medica Ateneo Parmense 2003; 74; 121-125

Review

Inhaled Steroids and Airway Remodelling in Asthma

Alfredo Chetta, Emilio Marangio, Dario Olivieri
Department of Clinical Sciences, Section of Respiratory Diseases, University of Parma, Italy

Abstract. Bronchial asthma is a chronic inflammatory disease characterized by inflammatory cell infiltration and by some long-lasting structural changes of bronchial wall, defined as airway remodelling. Airway remodelling can significantly affect two important functional characteristics of asthma, i.e. airway hyperresponsiveness and bronchial obstruction reversibility. Airway remodelling might be responsible for most of the inter-individual variability of bronchial hyperresponsiveness and might also determine the irreversible component of the airway obstruction, sometimes detectable in asthmatic patients. Among anti-asthma drugs, inhaled steroids are the most effective on inflammation and remodelling of airway wall. Recent evidences indicate that high doses of inhaled corticosteroids can significantly reduce not only inflammatory cells but also some components of airway remodelling, such as the increased airway wall vascularity and the basement membrane thickness. Conversely, low doses of inhaled corticosteroids can significantly act only on airway cell infiltration.

Key words: Asthma, airway remodelling, steroids

Introduction

Bronchial asthma is defined as a chronic inflammatory disease of airways (1). In asthma, airway inflammation is strictly related to bronchial hyperresponsiveness and variable airflow obstruction and can cause recurrent episodes of wheezing, breathlessness, chest tightness and cough (1).

Chronic inflammatory changes in asthma are characterized by airway wall accumulation of eosinophils, lymphocytes, mast cells, macrophages, dendritic cells, and myofibroblasts and by some structural changes of airway wall (2). These structural changes, defined as airway remodelling, are considered to result from increased activity of structural tissue components in an attempt at tissue repair following repetitive bouts of allergen (or other stimulus) -induced acute inflammatory changes and can play an important role in the pathophysiology of asthma (3). The airway remodelling consists in hypertrophy and hyperplasia of airway smooth muscle (4), increase in mucous glands (5), thickening of the reticular basement membrane (6), and qualitative and quantitative changes of airway blood vessels (7, 8) (Figure 1). Remodelling of the airway wall can occur not only in asthma but also in other chronic airway diseases, such as chronic obstructive pulmonary disease (COPD), however there are some differences between asthma and COPD in the affected structures and the prime anatomic site at which airway remodelling occurs (Table 1).

This overview describes the functional consequences of airway remodelling in bronchial asthma and its treatment.

Functional Implications

Bronchial hyperresponsiveness

Bronchial hyperresponsiveness is a well-established hallmark of airway function in asthma and is defined by an exaggerated response of the airways to non

Table 1. Characteristics of airway wall remodelling in asthma and COPD

	Asthma	COPD
Epithelium	Fragile	Metaplastic
Reticular Basement Membrane	Thickened	Not Thickened
Fibrosis	Unlikely	Present
Angiogenesis	Present	Likely
Bronchial Smooth Muscle	Increased (Large Airway)	Increased (Small Airway)
Glands	Hypertrophy	Hypertrophy

specific stimuli, which results in airway obstruction. Bronchial hyperresponsiveness is present in almost all patients with asthma, at least when they are having current symptoms. The two main determinants of bronchial hyperresponsiveness are an increase in *reactivity* as well as *sensitivity* of the airways (9). The increased *sensitivity* is reflected in a leftward shift of the dose-response curve to the bronchoconstritor stimulus. The increase in *reactivity* describes the increased degree of maximal airway narrowing, which is quite characteristic of asthma.

The airway remodelling is considered to contribute significantly to both components of bronchial hyperresponsiveness. Computational models suggest that the increase in thickness of each layer has the potential to contribute to bronchial hyperresponsiveness by a different mechanism. Firstly, the adventitial thickening can attenuate the load on airway smooth muscle which is provided by lung elastic recoil. Secondly, the thickening of the inner wall can amplify the effects of airway smooth muscle shortening. Finally, the increased muscle may increase the force generating capacity of the muscle, allowing it to overcome the elastic loads provided by lung recoil, airway mucosal folding and radial constraint (10).

Whether these computational models are applicable in chronic asthma remains to be proven, even if some methodological problems could limit this applicability. Firstly, direct histological assessment of remodelling *in vivo* studies is limited to evaluation of thickness of the subepithelial fibrosis in bronchial biopsies in central airways. Moreover, correct reading of the degree of subepithelial fibrosis is methodologically difficult (11). Lastly, bronchial hyperresponsiveness is generally expressed as the provocative concentration of methacholine causing the 20 percent fall of the forced expiratory volume at 1st second (PC_{20} FEV_1). However, the PC_{20} FEV_1 does not allow to distinguish between reactivity and sensitivity of airways (12). These methodological limitations can explain also conflicting results on relationship between bronchial hyperresponsiveness and airway remodelling. In fact, in some studies relationship was found (13-15), in another study this relationship was not confirmed (16). Additionally, when measured by high resolution CT scan, thickness of airway wall was not related to bronchial hyperresponsiveness (17).

Reversibility of airflow obstruction

Asthma is characterized by bronchial airflow obstruction which can be reversible both spontaneously and after treatment. Although in most asthmatic patients, bronchial airflow obstruction is completely reversible after bronchodilator and/or corticosteroid treatment, in patients with severe disease an irreversible component of the airway obstruction can be observed (18). Furthermore, this irreversible component of the airway obstruction can be shown even in asthmatic patients without any symptoms and in clinical remission (19). Moreover, bronchial asthma is associated with an increase in the rate of decline in respiratory parameters. Particularly, it has been demonstrated that the longitudinal decline in FEV_1 is more than 80% greater in asthmatic than in non asthmatic subjects (20).

To date there are no prospective studies providing evidence that structural changes, lung function parameters and respiratory symptoms are longitudinally related to asthma. However, it has been shown that the clinical and functional severity of asthma is directly associated with the thickening of the reticular basement membrane (6).

Table 2. Effects of anti-asthma drugs on airway remodelling in asthma

Effect	Steroids	Long-acting β_2-agonists	Leukotriene receptor antagonists
Epithelium Protection	yes	yes	not known
RBM Thickness Reduction	yes	no	not known
Inhibition of BSM proliferation	no	yes	yes
Vascularity Inhibition	yes	not known	not known
Edema Reduction	yes	yes	yes

RBM = Reticular Basement Membrane; BSM = Bronchial Smooth Muscle

Treatment

According to the current international guidelines, the therapeutic control of asthma is based on inhaled steroids, long-acting β_2-agonists and leukotriene receptor antagonists administration (1). Among anti-asthma drugs, several evidences show that inhaled steroids are the most effective on inflammatory process. Particularly, inhaled steroids are able to down-regulate several airway inflammatory cytokines (21), to reduce cell infiltration of bronchial wall (22), and may have some *in vitro* anti-angiogenic properties, because they directly inhibit the expression of the *vascular endothelial growth factor* gene (23).

Inhaled steroids are also the most effective drugs on airway remodelling in asthma (Table 2). Interestingly, these drugs seem to act in a dose-response fashion. Hoshino et al (24) showed that 800 μg beclomethasone dipropionate reduced airway wall vascularity in asthmatic patients. Orsida et al. (25) showed an effect of inhaled steroids on airway wall vascularity only above 500 μg of beclomethasone dipropionate. Moreover, another study by the same authors (26) failed to demonstrate any effect of three months treatment with a daily dose of 100 μg bid of fluticasone propionate plus a background dose of inhaled steroids (200-500 μg/day of beclometasone or 200-400 μg/day of budesonide) on vascularity in asthmatic patients. In order to reduce the basement membrane thickness of asthmatic patients, high doses of inhaled steroids, such as fluticasone propionate given at 250 μg bid (27) or at 750 μg bid (28) and beclometasone at 400 mg bid (24) or at 500 μg bid (29), can be effective. On the other hand, lower doses of inhaled steroids, such as budesonide 200 μg bid, did not demonstrate any effect on the thickening of basement membrane, despite a significant change in airway mucosal inflammation (30).

In a recent study, we provided evidence that bronchial responsiveness to methacholine, asthma symptom score and inflammatory cells decreased significantly after both low (100 μg twice a day) and high (500 μg twice a day) dose of fluticasone propionate. Moreover, the airway remodelling features, such as the increase in number of vessels and in the vascular area and the basement membrane thickness, decreased only after high dose of fluticasone propionate (31).

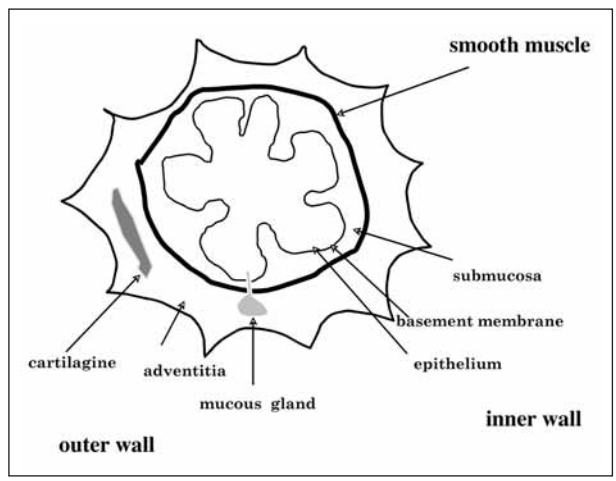

Figure 1. Schematic representation of the airway wall. The structural changes defined as airway remodelling involve both the inner and the outer wall and the airway smooth muscle. Particularly, airway remodelling consists in hypertrophy and hyperplasia of airway smooth muscle, increase in mucous glands, thickening of the reticular basement membrane, and qualitative and quantitative changes of airway blood vessels

Conclusions

In the last decade, increasing evidences have shown that airway remodelling is a constant morphological feature of chronic asthma. Though, the precise functional consequences of airway remodelling in asthma are still largely unknown, however several studies support the view that airway remodelling can play an important role on bronchial hyperresponsiveness and bronchial reversibility of airflow obstruction. In particular, even if bronchial hyperresponsiveness could not be dependent only on structural airway changes within airways, however airway remodelling might be responsible for most of the interindividual variability of bronchial hyperresponsiveness. Moreover, though the influence of the incomplete reversibility of airflow obstruction on the natural history of asthma is not yet well established, however, it is likely to assume that the residual airway obstruction sometimes detectable in asthmatic patients, may be associated with the remodelling of airway wall.

Inhaled steroids are quite effective on inflammatory changes of airway wall in asthma. The studies on this topic indicate that high doses of inhaled corticosteroids can significantly reduce not only inflammatory cells but also some components of airway remodelling, such as the increased airway wall vascularity and the basement membrane thickness. Conversely, low doses of inhaled corticosteroids can significantly act only on airway cell infiltration.

References

1. WHO/NHLBI Workshop Report: 1995. Global strategy for asthma management and prevention. National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD. Publication No. 95-3659.
2. Bousquet J, Jeffery PK, Busse WW, et al. State of art. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000; 161: 1720-45.
3. Kips IC, Pauwels RA. Airway wall remodelling: does it occur and what does it mean. *Clin Exp Allergy* 1999; 29: 1457-66.
4. Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993; 147: 405-10.
5. Takizawa T, Thurlbeck WM. Muscle and mucous gland size in the major bronchi of patients with chronic bronchitis, asthma, and asthmatic bronchitis. *Am Rev Respir Dis* 1971; 104: 331-6.
6. Chetta A, Foresi A, Del Donno M, et al. Airways remodeling is a distinctive feature of asthma and is related to severity of disease. *Chest* 1997; 111: 852-7.
7. Dunnill MS. The pathology of asthma with special reference to changes in the bronchial mucosa. *J Clin Pathol* 1960; 13: 27-33.
8. Li X, Wilson JW. Increased vascularity of the bronchial mucosa in mild asthma. *Am J Respir Crit Care Med* 1997; 156: 229-33.
9. Woolcock AJ, Salome CM, Yan K. The shape of the dose-response curve to histamine in asthmatic and normal subjects. *Am Rev Respir Dis* 1984; 130: 71-5.
10. King GG, Paré PD, Seow CY. The mechanics of exaggerated airway narrowing in asthma: the role of smooth muscle. *Respir Physiol* 1999; 118: 1-13.
11. Sullivan P, Stephens D, Ansari T, et al. Variation in the measurements of basement membrane thickness and inflammatory cell number in bronchial biopsies. *Eur Respir J* 1998; 12: 811-5.
12. Lötvall J, Inman N, O' Byrne P. Measurement of airway hyperresponsiveness: new considerations. *Thorax* 1998; 53: 419-24.
13. Chetta A, Foresi A, Del Donno M, et al. Bronchial responsiveness to distilled water and methacholine and its relationship to inflammation and remodeling of the airways in asthma. *Am J Respir Crit Care Med* 1996; 153: 910-7.
14. Hoshino M, Nakamura Y, Sim JJ, et al. Inhaled corticosteroid reduced lamina reticularis of the basement membrane by modulation of insulin-like growth factor (IGF)-1expression in bronchial asthma. *Clin Exp Allergy* 1998; 28: 568-77.
15. Laprise C, Laviolette M, Boutet M, et al. Asymptomatic airway hyperresponsiveness: relationship with airway inflammation and remodelling. *Eur Respir J* 1999; 14: 63-73.
16. Brewster CE Howarth PH, Djukanovic R, et al. Myofibroblasts and subepithelial fibrosis in bronchial asthma. *Am J Respir Cell Mol Biol* 1990; 3: 507-11.
17. Boulet LP, Belanger M, Carrier G. Airway responsiveness and bronchial-wall thickness in asthma with or without fixed airflow obstruction. *Am J Respir Crit Care Med* 1995; 152: 865-71.
18. Hudon C, Turcotte H, Laviolette M, et al. Characteristics of bronchial asthma with incomplete reversibility of airflow obstruction. *Ann Allergy Asthma Immunol* 1997; 78: 195-202.
19. Cade J and Pain M. Pulmonary function during clinical remission of asthma: how reversible is asthma? *Aust NZJ Med* 1973; 3: 545-51.
20. Peat JK, Woolcock AJ, Cullen K. Rate of decline of lung function in subjects with asthma. *Eur J Respir Dis* 1987; 70: 171-9.
21. Wang JH, Trigg CJ, Devalia JL, et al. Effect of inhaled beclomethasone dipropionate on expression of proinflammatory cytokines and activated eosinophils in the bronchial epithelium of patients with mild asthma. *J Allergy Clin Immunol* 1994; 94: 1025-34.

22. Booth H, Richmond I, Ward C, et al. Effect of high dose inhaled fluticasone propionate on airway inflammation in asthma. *Am J Respir Crit Care Med* 1995; 152: 45-52.
23. Nauck M, Karakiulakis G, Perruchoud AP, et al. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. *Eur J Pharmacol* 1998; 341: 309-15.
24. Hoshino M, Takahashi M, Takai Y, et al. Inhaled corticosteroids decrease vascularity of the bronchial mucosa in patients with asthma. *Clin Exp Allergy* 2001; 31: 722-30.
25. Orsida BE, Li X, Hickey B, et al. Vascularity in asthmatic airways: relation to inhaled steroid dose. *Thorax* 1999; 54: 289-95.
26. Orsida BE, Ward C, Li X, et al. Effect of a long-acting β_2-agonist over three months on airway wall vascular remodeling in asthma. *Am J Respir Crit Care Med* 2001; 164: 117-21.
27. Olivieri D, Chetta A, Del Donno M, et al. Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: a placebo-controlled study. *Am J Respir Crit Care Med* 1997; 155: 1864-71.
28. Ward C, Pais M, Bish R, et al. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax* 2002; 57: 309-16.
29. Trigg CJ, Manolitsas ND, Wang J, et al. Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. *Am J Respir Crit Care Med* 1994; 150: 17-22.
30. Jeffery PK, Godfrey RW, Adelroth E, et al. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. *Am Rev Respir Dis* 1992; 145: 890-9.
31. Chetta A, Zanini A, Foresi A, et al. Vascular component of airway remodeling in asthma is reduced by high dose of fluticasone. *Am J Respir Crit Care Med* 2003; 167: 751-7.

Received: 13 October 2003
Accepted in original form: 30 October 2003
Correspondence: Dr. Alfredo Chetta
Dipartimento di Scienze Cliniche,
Sezione di Clinica Pneumologica
Padiglione Rasori, Azienda Ospedaliera di Parma
Viale G. Rasori 10
43100 Parma, Italy
Tel: +39 0521 703 475
Fax: +39 0521 292 615
E-mail: chetta@unipr.it