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COX-2 expression in asthmatic airways: the story so far

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Cyclo-oxygenase (COX), also known as prostaglandin H synthase (PGHS), is the rate limiting enzyme for the conversion of arachidonic acid to prostanoids and exists in two isoforms. COX-1 is constitutively expressed and is responsible for the basal production of prostanoids, whereas COX-2 is highly inducible by a number of stimuli including cytokines and is associated with inflammation. Accumulating evidence suggests that the induction and regulation of COX-2 may be key elements in the pathophysiological process of a number of inflammatory disorders and may play an important role in the pathogenesis of asthma.[1]

Bronchoalveolar lavage fluid from patients with symptomatic asthma contains significantly increased levels of a number of proinflammatory cytokines including interleukin 1β and tumour necrosis factor α.[2 3] It has recently been shown that these proinflammatory cytokines are capable of inducing COX-2 in a number of cultured airway cells including airway epithelial cells,[4 5] airway smooth muscle cells,[6 7] and airway fibroblasts.[8] In addition, we have shown that transforming growth factor β_1 and the proinflammatory asthmatic mediator bradykinin also induce COX-2 in human airway smooth muscle cells.[9 10] These results suggest that COX-2 expression may be upregulated in asthmatic airways.

Several studies have examined COX-2 expression in asthmatic airways but the data are conflicting. Demoly *et al*[11] found that COX-2 was expressed in normal human respiratory epithelium and was not quantitatively upregulated in stable asthma. Conversely, Sousa and coworkers found increased expression of COX-2 in the epithelium and submucosa of asthmatic patients compared with control subjects.[12] Similarly, Taha and colleagues reported greater COX-2 immunoreactivity in the induced sputum, the submucosal inflammatory infiltrate, and the airway epithelium of patients with asthma than of unaffected control subjects.[13] Since corticosteroids have been shown in vitro to inhibit COX-2 expression in various airway cells,[4–9] the fact that the majority of asthmatic subjects in these studies were receiving treatment with inhaled corticosteroids at various doses may largely explain the discrepancies between these studies. In this issue of *Thorax* Redington *et al*[14] have made a fresh contribution to the study of COX-2 expression in asthma. Aware of the potential confounding effect of corticosteroids on COX-2 expression, they obtained bronchial biopsy specimens from three groups of subjects: atopic asthmatics treated with β_2 agonists alone, atopic asthmatics additionally receiving regular treatment with corticosteroids, and non-asthmatic control subjects. They found that the expression of both COX-2 mRNA and immunoreactive protein was increased in the airway epithelium of non-steroid treated asthmatics compared with non-asthmatic control subjects, and that the expression of COX-2 in asthmatic subjects receiving regular treatment with corticosteroids was not significantly different from that observed in non-asthmatic controls. Their findings clearly demonstrate that COX-2 is upregulated in the airway epithelium of asthmatic subjects and downregulated by corticosteroid treatment, and further strengthen the hypothesis that COX-2 may play a major role in the pathogenesis of asthma.

Since we and others[6 7 9] have shown that COX-2 is markedly induced in airway smooth muscle cells in vitro by proinflammatory cytokines and other mediators that exist in asthmatic airways, it is reasonable to speculate that COX-2 expression in airway smooth muscle is also upregulated in asthma. It would be important to study COX-2 expression in airway smooth muscle of asthmatic subjects as it is an important component of the airways and plays a crucial part in the pathophysiology of asthma.

The consequences of increased COX-2 expression in asthma are not clear. PGE_2, the main product of COX-2 induction, is an important anti-inflammatory mediator which has considerable bronchoprotective effects in the airways.[15] It is possible that PGE_2 production as a result of COX-2 induction may exert a braking effect on the inflammatory process in asthmatic airways. However, PGE_2 at higher concentrations also causes contraction of airway smooth muscle via thromboxane receptors.[16] PGD_2, $PGF_{2\alpha}$, and thromboxane A_2 are also potent bronchoconstrictors via thromboxane receptors.[16 17] PGI_2 causes relaxation of isolated precontracted human bronchus[12] but has little effect on airway calibre in vivo.[18]

Several studies of the effect of COX-2 induction on airway functions have been conducted. Gavett *et al* showed that allergen induced inflammation was increased in COX-2 deficient mice.[19] Belvisi *et al* reported that PGE_2 from COX-2 induction in airway smooth muscle inhibited cell proliferation.[20] We found that PGE_2 release after COX-2 induction mediated IL-1β and bradykinin induced attenuation of human airway smooth muscle cyclic AMP generation in response to β agonists,[21 22] and that PGE_2 from both COX-1 and COX-2 also largely mediated bradykinin stimulated IL-8 release from human airway smooth muscle cells.[23] These results suggest that COX-2 induction exerts both protective and proinflammatory effects. The consequences of increased COX-2 expression

in asthma are therefore likely to be complex and depend on the balance between the proinflammatory and the anti-inflammatory effects of prostanoids produced by various cell types under different circumstances. A better understanding of this issue might be achieved by direct functional studies with airway tissues from asthmatic patients, but these are notoriously difficult to obtain.

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Sarcoidosis: old and new treatments

G J Gibson

2001 marks the 50th anniversary of the first reports of the successful treatment of sarcoidosis with cortisone[1 2] and ACTH.[3] In an early report of treatment with corticosteroids, Siltzbach[4] highlighted one of the problems of evaluating the results when he wrote:

> "The aetiology of sarcoidosis still eludes us, as does the definitive treatment. Part of the difficulty stems from the unpredictability of spontaneous remissions. This accounts for the many transitory successes reported at one time or another with such agents as calcium salts, gold, arsenicals, potassium iodide, chaulmoogra oil, antileprol and tuberculin."

It is somewhat depressing that no better therapeutic agents than steroids have emerged over the subsequent 50 years, and the sceptic might well conclude that little has changed! While the approach to treatment may have become more rational and the choice of effective agents has increased, it is at best suppressive rather than curative. Happily, as Siltzbach pointed out, in most patients the natural tendency of pulmonary sarcoidosis is towards spontaneous resolution. The therapeutic challenges remain the recognition of those patients in whom remission and resolution are less likely, and determination of the optimum treatment to minimise permanent organ damage.

Several uncontrolled and controlled studies, as well as common clinical experience, have amply confirmed the suppressive effect of steroids.[5–11] In pulmonary sarcoidosis the most common indication for treatment is symptomatic, usually troublesome breathlessness and sometimes cough. Most commonly, prednisolone is started at a dose of 30–40 mg daily with later reduction titrated against symptoms, respiratory function, and radiographic appearance. Once started, treatment is usually continued for at least 1 year but patients may require more prolonged treatment if dose reduction is accompanied by recrudescence of disease activity. Whether or not steroid treatment reduces long term pulmonary damage due to fibrosis has proved difficult to determine. Common experience shows that in many cases pulmonary fibrosis is not prevented by steroids as, not infrequently, patients are seen with advanced destructive fibrosis even after their continuous use for several years. Most of the controlled studies which have attempted to assess the long term outcome of steroid treatment have been criticised on one or more counts—in particular, inclusion of patients with bilateral hilar lymphadenopathy without pulmonary shadowing, which has a good prognosis for spontaneous resolution, and the introduction of steroids at the time of presentation often in relatively asymptomatic patients in whom most clinicians would normally adopt a "wait and see" policy before embarking on treatment. The importance of the latter approach was apparent in the recent BTS controlled study[11] where 50% of patients who presented with pulmonary shadowing but