British Journal of Pharmacology (2003) 138, 1181–1182
www.nature.com/bjp

COMMENTARY

Extracellular matrix composition influences the resistance of airway remodelling events towards glucocorticoid treatment

[1]Simon Pitchford & *,[1]Clive Page

[1]Sackler Institute of Pulmonary Pharmacology, GKT School of Biomedical Science, King's College London 5th Floor, Hodgkin Building, London SE1 9RT

British Journal of Pharmacology (2003) **138,** 1181–1182. doi:10.1038/sj.bjp.0705136

Keywords: Asthma; laminin; collagen; smooth muscle; airway hyper-responsiveness

Abbreviations: AHR, airways hyperresponsiveness; bFGF, basic fibroblast growth factor; DNA, deoxyribose nucleic acid; ECM, extra-cellular matrix; GCS, glucocorticoids

It is now well recognised that various; aspects of remodelling are present in the lungs of subjects with asthma, including increased airway smooth muscle mass (Carroll *et al*., 1993). These events have been suggested to contribute to increased airway sensitivity and reactivity to spasmogens, exaggerating increases to airway resistance (James *et al*., 1989). From mathematical studies of airway tissue (Wiggs *et al*., 1992), increased airway smooth muscle mass is thought to contribute directly to the airway hyper-responsiveness (AHR) that is a characteristic of asthma (Lambert *et al*., 1993), although this contribution has not been supported in experimental studies (Woisin *et al*., 2001).

It is also now recognised that while glucocorticoids (GCS) are the most effective drugs used in the long-term treatment of asthma, there being a reduction in AHR attributed to the reversal of inflammatory cell infiltration and activation of the lungs (Ward *et al*., 2002), a loss of functional reversibility is apparent in some individuals (Ward *et al*., 2002). Asthmatics still exhibit AHR following even prolonged treatment with GCS, suggesting an irreversible component to asthma that is not affected by treatment with these drugs (Lundgren *et al*., 1988; Ward *et al*., 2002).

Few long-term studies have been conducted in asthmatic patients, quantifying changes in airway structure following GCS therapy. However, it would appear that structural changes are not altered to any great extent with GCS treatment in patients with asthma (Boulet *et al*., 2000). This has also been demonstrated in experimental models of chronic allergic airway inflammation, where repeated allergen exposure of sensitised Brown–Norway rats induced DNA synthesis in airway smooth muscle and epithelial cells (Salmon *et al*., 1999), while treatment with fluticasone dipropionate postallergen exposure did not reverse established alterations to the airways in a similar animal model (Vanacker *et al*., 2001). Furthermore, regular treatment of allergic rabbits with GCS failed to reverse baseline AHR (El Hashim *et al*., 1999), despite such drugs clearly inhibiting allergen-induced exacerbations of AHR in the same species (El Hashim *et al*., 1999). However, our understanding of why GCS do not completely reverse these chronic changes in asthma is not fully understood.

In this current issue of the *British Journal of Pharmacology*, Bonacci *et al*. have attempted to reveal a potential mechanism by which airway smooth muscle hyperplasia may be resistant to the antimitogenic actions of GCS during chronic episodes of asthma. Their studies compared the ability of two GCS, dexamethasone and fluticasone propionate, to inhibit the growth of airway smooth muscle cells on both laminin- and collagen-coated surfaces after being stimulated by basic fibroblast growth factor (bFGF). Their results have revealed that the antimitogenic actions of GCS administration to smooth muscle cells grown on laminin were not mimicked when airway smooth muscle cells were grown on collagen. The reasons why smooth muscle cells grown on collagen-coated surfaces should be resistant to the antimitogenic actions of GCS, however, remain unknown. *In vitro* studies investigating the effects of GCS on smooth muscle growth have largely been conducted on plastic plates (Stewart *et al*., 1995), despite the knowledge that airway smooth muscle growth is influenced by the extracellular matrix (ECM) (Stewart, 2001), the composition of which changes in asthmatic individuals where collagen becomes a greater component (Roche *et al*., 1989). Importantly, studies in asthmatic patients have demonstrated no significant alteration in subepithelial fibrosis or types I and III collagen deposition within the ECM after treatment with GCS (Boulet *et al*., 2000), providing a basis by which smooth muscle hyperplasia and therefore a loss of functional reversibility to the lungs, even after GCS therapy, may occur in some asthmatics. Future studies are clearly needed to reveal the exact nature and mechanisms by which collagen is deposited within the ECM, and this current research by Bonacci *et al*., suggests that this pathway is worthy of further studies if we are to improve the treatment of asthma beyond GCS.

*Author for correspondence; E-mail: clive.page@kcl.ac.uk

References

BOULET, L.P., TURCOTTE, H., LAVIOLETTE, M., NAUD, F., BERNIER, M.C., MARTEL, S. & CHAKIR, J. (2000). Airway hyperresponsiveness, inflammation, and subepithelial collagen deposition in recently diagnosed versus long-standing mild asthma. Influence of inhaled corticosteroids. *Am. J. Respir. Crit. Care Med.,* **162,** 1308–1313.

CARROLL, N., ELLIOT, J., MORTON, A. & JAMES, A. (1993) The structure of large and small airways in nonfatal and fatal asthma. *Am. Rev. Respir. Dis.,* **147,** 405–410.

EL HASHIM, A.Z., BANNER, K.H., PAUL, W. & PAGE, C.P. (1999). Effects of dexamethasone on airway hyper-responsiveness to the adenosine A1 receptor agonist cyclo-pentyl adenosine in an allergic rabbit model. *Br. J., Pharmacol.,* **126,** 1513–1521.

JAMES, A.L., PARE, P.D. & HOGG, J.C. (1989). The mechanics of airway narrowing in asthma. *Am. Rev. Respir. Dis.,* **139,** 242–246.

LAMBERT, R.K., WIGGS, B.R., KUWANO, K., HOGG, J.C. & PARE, P.D. (1993). Functional significance of increased airway smooth muscle in asthma and COPD. *J. Appl. Physiol.,* **74,** 2771–2781.

LUNDGREN, R., SODERBERG, M., HORSTEDT, P. & STENLING, R. (1988). Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. *Eur. Respir. J.,* **1**, 883–889.

ROCHE, W.R., BEASLEY, R., WILLIAMS, J.H. & HOLGATE, S.T. (1989). Subepithelial fibrosis in the bronchi of asthmatics. *Lancet*, **1,** 520–524.

SALMON, M., WALSH, D.A., KOTO, H., BARNES, P.J. & CHUNG, K.F. (1999). Repeated allergen exposure of sensitized Brown–Norway rats induces airway cell DNA synthesis and remodelling. *Eur. Respir. J.,* **14,** 633–641.

STEWART, A.G. (2001). Airway smooth muscle as a target for novel antiasthma drugs acting on airway wall remodelling. In: *Lung Biology in Health and Disease*. eds. Howarth, P.H., Wilson, J.W., Bousquet, J., Rak, S. & Pauwels, R.A. pp. 217–243. New York: Marcel Dekker Inc.

STEWART, A.G., FERNANDES, D. & TOMLINSON, P.R. (1995). The effect of glucocorticoids on proliferation of human cultured airway smooth muscle. *Br. J. Pharmacol.,* **116,** 3219–3226.

VANACKER, N.J., PALMANS, E., KIPS, J.C., PAUWELS, R.A. (2001). Fluticasone inhibits but does not reverse allergen-induced structural airway changes. *Am. J. Respir. Crit. Care. Med.,* **163,** 674–679.

WARD, C., PAIS, M., BISH, R., REID, D., FELTIS, B., JOHNS, D. & WALTERS, E.H. (2002). Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax,* **57,** 309–316.

WIGGS, B.R., BOSKEN, C., PARE, P.D., JAMES, A. & HOGG, J.C. (1992). A model of airway narrowing in asthma and in chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.,* **126,** 1513–1521.

WOISIN, F.E., HERD, C.M., DOUGLAS, G.J., RAYNOR, K., SPINA, D., MITCHELL, H.W. & PAGE, C.P. (2001). Relationship of airway responsiveness with airway morphometry in normal and immunized rabbits. *Pulm. Pharmacol. Ther.,* **14,** 75–83.

(Received November 27, 2002
Accepted December 9, 2002)