British Journal of Pharmacology (2008) 153, 1085–1086
 0007–1188/08 $30.00
www.brjpharmacol.org

COMMENTARY

Combining inhaled glucocorticoids and long acting β_2-adrenoceptor agonists in asthma and COPD

AJ Knox and K Mortimer

Division of Respiratory Medicine, Centre for Respiratory Research, Clinical Sciences Building, City Hospital, Nottingham, UK

Inhaled long-acting β_2-adrenoceptor agonists and glucocorticoids form the mainstay of maintenance treatment of asthma and chronic obstructive pulmonary disease (COPD), usually given as a combination inhaler. Most patients will have good asthma control if they comply with this therapy, although it is generally less effective in COPD. The traditional dogma has been that these agents act on distinct components of disease pathophysiology with β_2 agonists acting on the bronchospastic component and glucocorticoids acting on the inflammatory component. Considerable evidence has emerged recently, however, to suggest that these two classes of agents interact at a molecular level. Understanding the mechanisms of these interactions may enable the development of new therapies for asthma and COPD.
British Journal of Pharmacology (2008) **153,** 1085–1086; doi:10.1038/bjp.2008.4; published online 28 January 2008

Keywords: asthma; COPD; β-agonist; glucocorticoid; interaction; airway

Airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) constitute a major health burden on a global scale. Chronic airway inflammation and abnormal repair are central features of the pathology of both diseases, although the inflammatory cells, cytokines and growth factors driving the processes are distinct (Tattersfield *et al*., 2002; Barnes *et al*., 2003). There has been considerable investment by the pharmaceutical industry in trying to develop novel, innovative therapies targeting specific components of the disease processes. Despite this effort, the mainstay of treatment remains two classes of molecules based on chemical modifications of endogenous stress hormones, namely, the β_2-adrenoceptor agonists and the glucocorticoids. Just as the physiological adrenal hormones act in a complementary manner so too, it would appear, their pharmacological counterparts.

Short-acting β_2-adrenoceptor agonists have been the main therapy for relief of asthma and are also used extensively in COPD. The development of the inhaled long-acting β_2-adrenoceptor agonists (LABAs), salmeterol and formoterol, have been an important addition to maintenance therapy for asthma, particularly in the management of persistent moderate to severe asthma but also in mild asthma (O'Byrne *et al*., 2001). Inhaled LABAs are most effective when given in conjunction with inhaled corticosteroids (ICS), and most patients with persistent asthma now receive both classes of treatment, in accordance with international guidelines for asthma management. This has led to the logical development of fixed combination inhalers that contain a LABA and ICS in the same inhaler device such as Seretide (salmeterol/fluticasone) and Symbicort (formoterol/budesonide).

There have now been numerous studies in asthma showing that when LABAs are given in conjunction with ICS, they produce beneficial effects on symptoms, airflow and asthma exacerbations and that this effect is greater than that can be achieved with doubling the dose of inhaled glucocorticoid. More recently studies from COPD (Calverley *et al*., 2007) have shown that this approach is also effective, although to a lesser degree and all of these studies are nicely reviewed in this issue of the *British Journal of Pharmacology* by Giembycz *et al*. (2008).

The mechanism underlying the complementary actions of the two classes of drugs has been the subject of intense debate. The traditional dogma has been that the β_2-adrenoceptor agonists target the airway smooth muscle contraction, which characterizes asthma and COPD, whereas the glucocorticoids act to suppress the inflammatory component and that the two classes of agents are acting independently on different aspects of the pathogenesis of the disease. This model, however, would not explain why there is a greater reduction in exacerbations of disease when LABAs are added to glucocorticoid therapy, and this suggests that additional actions and, more particularly, interactions are important. A more likely explanation is that these two classes of drugs are interacting in a beneficial manner, and there is now a wealth of data from studies *in vitro* and more recently *in vivo* to suggest that this is indeed the case. Giembycz *et al*. provide a thorough review of these studies showing that these agents can interact in multiple ways on

Correspondence: Professor AJ Knox, Centre for Respiratory Research, Division of Respiratory Medicine, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK.
E-mail:alan.knox@nottingham.ac.uk
Received 14 December 2007; accepted 17 December 2007; published online 28 January 2008

different aspects of the inflammatory and remodelling processes, which characterize airways diseases such as asthma and COPD. It is clear that there are multiple sites at which the drugs can act to potentiate each other's effects and that this can occur at several levels, such as inflammatory gene transcription (both transrepression and transactivation) and translation. A further layer of complexity is added by the fact that the drugs have different effects on individual inflammatory genes and in different cell types (that is, some genes are sensitive to these agents, whereas others are not and the effects may be cell-specific). The sensitivity of some genes and their products is likely to be determined by the transcription factors, chromatin changes and posttranscriptional processes involved. The maximum scope for interaction is probably in those airway cells with the largest number of β_2-adrenoceptors, such as airway smooth muscle, a cell type that has been recognized to function as a rich source of inflammatory and remodelling molecules in asthma (Johnson and Knox, 1997).

The potentiation of glucocorticoid effects by β_2-adrenoceptor agonists appears to be a class effect of these drugs when studied in cell systems *in vitro* and is seen with both short-acting and long-acting drugs (Pang and Knox, 2001, Knox, 2002). In contrast, when studied *in vivo*, short-acting drugs do not seem to have the same beneficial effects on long-term disease control as LABAs. The most likely explanation for this discrepancy is that when drugs are studied *in vitro*, they are not usually washed out of the experimental system, so that short-acting β_2-adrenoceptor agonists behave similarly to long-acting ones. *In vivo*, however, the different pharmacokinetics mean that beneficial effects are lost with short-acting drugs. Indeed, rebound worsening of asthma has been shown with cessation of short-acting β_2-agonist therapy (Vathenen *et al.*, 1988), which is not seen with LABAs.

In summary, the excellent review by Giembycz *et al.* highlights our greater understanding of the mechanisms of action of the two main classes of asthma and COPD therapies. Perhaps, equally important in the future, however, if we are to develop more effective therapies, will be to get a better understanding of why some processes are sensitive to these drugs and yet others are not.

References

Barnes PJ, Shapiro SD, Pauwels RA (2003). Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur Respir J* **22**: 672–688.

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW *et al.* (2007). Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* **356**: 775–789.

Giembycz MA, Kaur M, Leigh R, Newton R (2008). A Holy Grail of asthma management: toward understanding how long-acting β_2-adrenoceptor agonists enhance the clinical efficacy of inhaled corticosteroids. *Br J Pharmacol* **153**: 1090–1104 (this issue).

Johnson SR, Knox AJ (1997). Synthetic functions of airway smooth muscle in asthma. *Trends Pharmacol Sci* **18**: 288–292.

Knox AJ (2002). The scientific rationale of combining inhaled glucocorticoids and long acting beta 2 adrenoceptor agonists. *Curr Pharm Des* **8**: 1863–1869.

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K *et al.* (2001). Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* **164**: 1392–1397.

Pang L, Knox AJ (2001). Regulation of TNF-alpha-induced eotaxin release from cultured human airway smooth muscle cells by beta2-agonists and corticosteroids. *FASEB J* **15**: 261–269.

Tattersfield AE, Knox AJ, Britton JR, Hall IP (2002). Asthma. *Lancet* **360**: 1313–1322.

Vathenen AS, Knox AJ, Higgins BG, Britton JR, Tattersfield AE (1988). Rebound increase in bronchial responsiveness after treatment with inhaled terbutaline. *Lancet* **1**: 554–558.