different segmentation algorithms and observer training levels. *Eur J Radiol* 2007;**64**:285–95.
9. **Shinagawa N,** Yamazaki K, Onodera Y, *et al*. Factors related to diagnostic sensitivity using an ultrathin bronchoscope under CT guidance. *Chest* 2007;**131**:549–53.
10. **Vincent BD,** Fraig M, Silvestri GA. A pilot study of narrow-band imaging compared to white light bronchoscopy for evaluation of normal airways and premalignant and malignant airways disease. *Chest* 2007;**131**:1794–9.
11. **Coxson HO,** Quiney B, Sin DD, *et al*. Airway wall thickness assessed using computed tomography and optical coherente tomography. *Am J Respir Crit Care Med* 2008;**177**:1201–6.
12. **Shedden K,** Taylor JMG, Enkemann SA, *et al*. Gene expression-based survival prediction in lung adenocarcinoma: a multi-site, blinded validation study. *Nat Med* 2008;**14**:822–7.
13. **Spira A,** Beane JE, Shah V, *et al*. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. *Nat Med* 2007;**13**:361–6.
14. **Yanagisawa K,** Shyr Y, Xu BJ, *et al*. Proteomic patterns of tumour subsets in non-small-cell lung cancer. *Lancet* 2003;**362**:433–9.
15. **Yildiz PB,** Shyr Y, Rahman JSM, *et al*. Diagnostic accuracy of MALDI mass spectrometric análysis of unfractionated serum in lung cancer. *J Thorac Oncol* 2007;**2**:893–901.
16. **Brock MV,** Hooker CM, Ota-Machida E, *et al*. DNA methylation markers and early recurrence in stage I lung cancer. *N Engl J Med* 2008;**358**:1118–28.
17. **Maheswaran S,** Sequist LV, Nagrath S, *et al*. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med* 2008;**359**:1–12.
18. **Chapman CJ,** Murray A, McElveen JE, *et al*. Autoantibodies in lung cancer: possibilities for early detection and subsequent cure. *Thorax* 2008;**63**:228–33.
19. **Chen X,** Ba Y, Ma L, *et al*. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res* 2008;**18**:997–1006.
20. **Carpagnano GE,** Foschino-Barbaro MP, Spanevello A, *et al*. 3p microsatellite signature in exhaled breath condensate and tumor tissue of patients with lung cancer. *Am J Respir Crit Care Med* 2008;**177**:337–41.
21. **Mazzone PJ.** Analysis of volatile organic compounds in the exhaled breath for lung cancer diagnosis. *J Thorac Oncol* 2008;**3**:774–80.
22. **Westhoff M,** Litterst P, Freitag L, *et al*. Ion mobility spectrometry for the detection of volatile organic compounds in exhaled breath of patients with lung cancer: results of a pilot study. *Thorax* 2009;**64**:744–8.

The β_2 receptor and airway hyper-responsiveness: are sensory nerves involved?

Clive Page

The use of β_2 agonists for the control of symptoms is central to the treatment of patients with asthma. However, there is controversy surrounding the regular use of this drug class as numerous studies have demonstrated a variety of changes that can be considered unwanted attributes, particularly when these drugs are used regularly as monotherapy. These include increased bronchial hyper-responsiveness (BHR) to inhaled contractile agents[1] and an increase in the allergen-induced early[2] and late asthmatic response[3] following regular treatment with short-acting β_2 agonists (SABAs). Furthermore, a number of studies have suggested that regular treatment with inhaled SABAs and long-acting β_2 agonists (LABAs) by inhalation leads to a loss of bronchoprotection[4 5] and with salmeterol treatment an excess mortality in patients with asthma,[6] a trend also observed with regular treatment with formoterol.[7] This has led the Food and Drug Administration (FDA) to post black-box warnings on all medicines containing these LABAs.

Christian Virchow and colleagues from Rostock have provided data (***see page 763***) on a potential mechanism as to how regular treatment with salmeterol can paradoxically increase BHR.[8] Eighteen patients with mild allergic asthma inhaled standard doses of salmeterol xinafoate for 2 weeks, followed by 2 weeks of treatment with the combination of fluticasone and salmeterol xinafoate. There was no overall statistically significant change in BHR for the whole group receiving monotherapy with salmeterol. However, 67% of the patients showed a modest increase in BHR as measured by a lowered PC_{20} (provocative concentration of histamine causing a 20% fall in the forced expiratory volume in 1 s) following monotherapy with salmeterol compared with baseline. This contrasted with a statistically significant improvement in BHR following the combination therapy. The levels of brain-derived neurotrophic factor (BDNF) were elevated in both serum and platelets obtained from patients receiving monotherapy with salmeterol, and the changes in BDNF levels correlated with the changes in PC_{20}, although the levels of BDNF decreased significantly and there was no such correlation with changes in PC_{20} in the patients receiving the combination therapy. The changes in PC_{20} following monotherapy with inhaled salmeterol did not show a correlation with known β_2 receptor polymorphisms.

A number of other investigators have suggested a role for BDNF in BHR as this is a mediator that is increased in subjects with asthma, both in the lung[9] and in platelets,[10] and which at least in animal models can induce BHR associated with changes in neuronal activity.[11] In patients with asthma, the systemic levels of BDNF are also elevated, whilst they correlate with BHR.[9] Increases in BDNF levels in the lung following allergen challenge of patients with asthma can be reduced by glucocorticosteroids.[12] Airway sensory nerves have also been implicated in the pathogenesis of BHR induced by a number of stimuli,[13] including treatment with regular β_2 agonists,[14] and it is of particular interest that platelet activation has also been observed to play a central role in allergen-induced BHR experimentally,[15 16] supporting the observations of Virchow and colleagues in the present study. Interestingly, salmeterol enhanced the secretion of BDNF from tumour necrosis factor α (TNFα)-stimulated human peripheral blood mononuclear cells, whilst BDNF secretion was inhibited by fluticasone.

Clearly it would be of interest to see if salmeterol also caused an increase in BDNF secretion from platelets, thus allowing a clearer link between platelet activation, BDNF and the exacerbation of BHR observed following monotherapy with regular inhaled salmeterol. Whilst the acute benefits of β_2 agonist therapy are well accepted, the worsening of asthma control with chronic β_2 agonist treatment is not as well accepted, with a recent study reinforcing the safety of regular β_2 agonists use.[17] Nonetheless, a number of mechanisms have been put forward to explain worsening asthma control with regular β_2 agonist treatment, including increased antigen burden,[18] increased BHR induced by the (+) enantiomer[14] and loss of bronchoprotection.[4] Recently, the role of β_2 receptors in asthma has become more complicated with the recognition that β-blockers, which have traditionally been contraindicated in the treatment of patients with

Correspondence to: Professor Clive Page, Sackler Institute of Pulmonary Pharmacology, Division of Pharmaceutical Sciences, King's College London, Guy's Campus, London Bridge, London SE1 9RT, UK; clive.page@kcl.ac.uk

asthma, can improve BHR when administered chronically to patients with mild asthma.[19] This research has many parallels with the use of β-blockers in the treatment of patients with heart failure where this class of drug was once contraindicated as acute dosing produced adverse effects in such patients.[20] It was then subsequently recognised that chronic dosing with β-blockers was beneficial in patients with heart failure, and the use of this drug class is now considered a central part of standard treatment guidelines. So-called "paradoxical pharmacology",[21] where there may be differential effects of acute versus chronic dosing of a given class of drug, would seem to be a very important issue when considering the use of drugs that recognize the β_2 receptor.

Furthermore, given that it has been recently suggested that some β-blockers act as inverse agonists at the β_2 receptor and activate novel signalling pathways that are required for the full asthma phenotype in mice,[22] it would seem time to challenge the dogma that activation of β_2 receptors chronically is a good thing. If nothing else, the study by Virchow and colleagues provides further support for why monotherapy with β_2 receptor agonists has no role in the treatment of patients with asthma.

Competing interests: CP is a co-founder of Verona Pharma which has an interest in developing novel drugs for treating respiratory diseases.

Provenance and peer review: Commissioned; not externally peer reviewed.

Thorax 2009;**64**:738–739. doi:10.1136/thx.2009.113506

REFERENCES

1. **Page CP,** Spina D. Beta2-agonists and bronchial hyperresponsiveness. *Clin Rev Allergy Immunol* 2006;**31**:143–62.
2. **Cockcroft DW,** McParland CP, Britto, *et al*. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;**342**:833–37.
3. **Gauvreau GM,** Jordana M, Watson RM, *et al*. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Crit Care Med* 1997;**156**:1738–45.
4. **Cheung D,** Timmers MC, Zwinderman AH, *et al*. Long term effects of a long acting beta 2 adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992;**327**:1198–203.
5. **O'Connor BJ,** Aikman SL, Barnes PJ. Tolerance to the non-bronchodilator effects of inhaled beta 2 agonists in asthma. *N Engl J Med* 1992;**327**:1204–8.
6. **Nelson HS,** Weiss ST, Bleeker ER, *et al* The salmeterol multicentre asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;**129**:15–26.
7. **Sears MR,** Ottosson A, Radner F, *et al*. Long acting beta agonists: a review of formoterol safety data from asthma clinical trials. *Eur Resp J* 2009;**33**:21–32.
8. **Lommatzsch M,** Lindner Y, Edner A, *et al*. Adverse effects of salmeterol in asthma: a neuronal perspective. *Thorax* 2009;**64**:763–9.
9. **Virchow JC,** Julius P, Lommatzsch M, *et al*. Neurotrophins are increased in bronchoalveolar lavage fluid after segmental allergen provocation. *Am J Respir Crit Care Med* 1998;**158**:2002–5.
10. **Lommatzsch M,** Schloetcke K, Klotz J, *et al*. Brain-derived neurotrophic factor in platelets and airflow limitation in asthma. *Am J Respir Crit Care Med* 2005;**171**:115–20.
11. **Braun A,** Lommatzsch M, Neuhaus-Steinmetz U, *et al*. Brain-derived neurotrophic factor (BDNF) contributes to neuronal dysfunction in a model of allergic airway inflammation. *Br J Pharmacol* 2004;**141**:431–40.
12. **Noga O,** Hanf G, Schaper C, *et al*. The influence of inhalative corticosteroids on circulating nerve growth factor, brain-derived neurotrophic factor and neurotrophin-3 in allergic asthmatics. *Cli Exp Allergy* 2001;**31**:1906–12.
13. **Spina D,** Page CP. Asthma—a need for a rethink? *Trends Pharmacol Sci* 2002;**23**:311–5.
14. **Keir S,** Page C, Spina D. Bronchial hyperresponsiveness induced by chronic treatment with albuterol: role of sensory nerves. *J Allergy Clin Immunol* 2006;**118**:551–9.
15. **Coyle AJ,** Page CP, Atkinson L, *et al*. The requirement of platelets for allergen-induced late asthmatic airways obstruction. *Am Rev Respir Dis* 1990;**142**:587–93.
16. **Pitchford SC,** Riffo-Vasquez Y, Sousa A, *et al*. Platelets are necessary for airway wall remodeling in a murine model of chronic allergic inflammation. *Blood* 2004;**103**:639–47.
17. **Drazen JM,** O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. *N Engl J Med* 2009;**360**:1671–2.
18. **Page CP.** One explanation of the asthma paradox: inhibition of natural anti inflammatory mechanisms by beta 2-agonists. *Lancet* 1991;**337**:717–20.
19. **Hanania NA,** Singh S, El-Wali R, *et al*. The safety and effects of the beta blocker, nadolol, in mild asthma: an open label pilot study. *Pulm Pharmacol Ther* 2008;**21**:134–41.
20. **Bond R,** Spina D, Parra S, *et al*. Getting to the heart of asthma: can beta blockers be useful to treat asthma? *Pharmacol Ther* 2007;**115**:360–74.
21. **Bond RA.** Is paradoxical pharmacology a strategy worth pursuing? *Trends Pharmacol Sci* 2001;**22**:273–6.
22. **Nguyen LP,** Lin R, Parra S, *et al*. Beta2-adrenoceptor signaling is required for the development of an asthma phenotype in a murine model. *Proc Natl Acad Sci USA* 2009;**106**:2435–40.

Mechanisms of adverse effects of β-agonists in asthma

Sebastian L Johnston, Michael R Edwards

Short-acting β-agonist (SABA) drugs have been mainstays of asthma therapy for many decades and are recommended treatment at all levels of asthma severity, as they provide prompt relief of asthma symptoms through smooth muscle relaxation and, thereby, bronchodilatation. At all levels of asthma severity more severe than mild intermittent, SABAs are recommended to be taken as required for relief of symptoms in conjunction with inhaled corticosteroids (ICSs) taken as regular maintenance treatment. However, in mild asthma SABAs are recommended as monotherapy without concomitant ICS therapy, and in both mild and more severe asthma, greatly increased SABA use at times of asthma exacerbation is almost universal. Here we discuss the safety of inhaled β-agonist monotherapy in asthma and argue against the continued use of β-agonist monotherapy (both short and long acting) in the absence of concomitant ICS therapy in a combination inhaler.

Several epidemiological studies link overuse of SABA therapies at times of asthma exacerbation with increased risk of hospitalisation or mortality.[1 2] The mechanisms underlying this increased risk have not been clearly determined, but are most likely to involve complex mechanisms including delays in seeking medical care, potential cardiac (tachycardia) and metabolic (hypokalaemia) adverse effects as well as possible effects on underlying asthma severity. Although fenoterol, the SABA linked with the epidemic of asthma mortality in the early 1980s in New Zealand[3] and some other countries,[4] has greater cardiac effects than other SABAs, the reduction in hospitalisations due to asthma exacerbations (along with a reduction in asthma mortality) following the withdrawal of high dose fenoterol in New Zealand in 1990 suggested that the reduction in asthma mortality was not wholly due to reduction in cardiac/metabolic side effects, but probably also due to an effect on disease severity (because if the reduction in mortality were due to reduction in cardiac side effects, the rate of hospitalisations due to asthma exacerbations should have remained unchanged).[5]

Department of Respiratory Medicine, National Heart and Lung Institute, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, Imperial College London, London, UK

Correspondence to: Professor Sebastian L Johnston, Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College London, Norfolk Place, London W2 1PG, UK; s.johnston@imperial.ac.uk