ADENOSINE-INDUCED BRONCHOCONSTRICTION IN SENSITISED GUINEA PIGS: ROLE FOR SENSORY NERVES.

S.D. Rudman, D. Spina & C.P. Page. Sackler Institute of Pulmonary Pharmacology, GKT School of Biomedical Sciences, King's College London, SE1 9RT.

Inhaled adenosine induces bronchoconstriction in asthmatic but not healthy subjects (Cushley *et al*., 1985), thus providing a possible insight into the mechanism of airway hyperresponsiveness. Adenosine also induces bronchoconstriction in various animal species following immunisation, including the rabbit (El-hashim *et al*., 1996), the brown Norway rat (Hannon *et al.,* 1999) and the guinea pig (Thorne & Broadley 1994). Furthermore, responsiveness to adenosine in the immunised rabbit was shown to be A1 receptor mediated (El Hashim *et al*., 1996; Nyce & Metzger, 1997). The aims of the present study was to demonstrate bronchoconstriction to aerosolised adenosine 5' monophosphate (AMP) and A_1-receptor agonist cyclopentyl adenosine (CPA) in passively sensitised guinea pigs. The effect of chronic pre-treatment with capsaicin on this response was also investigated.

Male Dunkin-Harley guinea pigs (300-500g) were treated for 3 days with ascending doses of capsaicin (8-methyl-N-vanillyl-6-nonenamide; total 80mg/kg s.c.) or vehicle (1:1:8 ethanol; tween 80; saline). On the third day, guinea pigs were passively sensitised against ovalbumin (Ova). On day 10-12, animals were anaesthetised (urethane 1.5g/kg) and connected to a ventilator (4ml/kg; 60 breaths/min) via a tracheal cannula. The increase in total airways resistance above baseline (R_L; $cmH_2O/L/s$) and decrease in dynamic lung compliance (C_{dyn}; ml/cmH_2O) was measured in response to aerosolised AMP (10mg/ml), CPA (10mg/ml) and ova (5mg/ml). Capsaicin (100µg/kg) was injected intravenously at the end of the experiment to confirm desensitisation.

Results are expressed as mean $\pm$ s.e.m, n=5 for all treatment groups. Passively sensitised guinea pigs showed a significant increase in R_L (% increase above baseline) following aerosol exposure with AMP (33.3 $\pm$ 2.1), CPA (28.2 $\pm$ 3.1) and ova (32.5 $\pm$ 5.2) compared with naïve guinea pigs (AMP: 1.4 $\pm$ 0.3, CPA: 2.1 $\pm$ 0.9 and Ova 2.1 $\pm$ 1.1; $P<0.05$). Sensitised guinea pigs also exhibited a significantly greater decrease in C_{dyn} (AMP: 47.5 $\pm$ 7.5; CPA: 27.2 $\pm$ 0.2; Ova: 41.7 $\pm$ 4.4) compared with naïve animals (AMP 4.2 $\pm$ 1.5; CPA: 3.9 $\pm$ 0.9; Ova 2.7 $\pm$ 1.3; $P<0.05$). Furthermore, in passively sensitised guinea pigs chronically treated with capsaicin, the response to both AMP (R_L 5.2 $\pm$ 2.2; C_{dyn}: 4.2 $\pm$ 1.8; $P<0.05$) and CPA (R_L 7.0 $\pm$ 1.3; C_{dyn} 5.1 $\pm$ 1.1; $P<0.05$) was significantly inhibited.

We have demonstrated that both AMP and CPA cause bronchoconstriction in passively sensitised but not naïve guinea pigs. Furthermore, we have shown that chronic pre-treatment with capsaicin inhibits AMP- and CPA-induced bronchoconstriction. This suggests that bronchoconstriction to adenosine in sensitised guinea pigs involves the activation of capsaicin-sensitive nerves.

Cushley M.J. *et al.,* 1985, Eur. J. Respir. Dis 67:185-192
El-hashim A. *et al* 1996, Br. J. Pharmacol 119: 1262-1268
Hannon *et al* 1999, Br. J. Pharmacol 132:1509-1523
Nyce J.W. & Metzger W.J., 1997 Nature 385: 721-725
Thorne J.R. & Broadley K.R., 1994 Am.J.Respir.Crit.Care Med 149: 392-399

This project is supported by GlaxoSmithKline, U.K.