References

BEUMER, H.M. (1971). Comparative studies of the protective effect of Alupent and Th1165A against histamine in man. *Respiration*, **28**, 148-157.

BOWMAN, W.C. & NOTT, M.W. (1970). Actions of some sympathomimetic bronchodilator and beta-adrenoceptor blocking drugs on contractions of the cat soleus muscle. *Br. J. Pharmac.*, **38**, 37-49.

JAMES, G.W.L. (1969). The use of the *in vivo* trachea preparation of the guinea-pig to assess drug action on lung. *J. Pharm. Pharmac.*, **21**, 379-386.

LEGGE, J.S., GADDIE, J. & PALMER, K.N.V. (1971). Comparison of two oral selective β_2-adrenergic stimulant drugs in bronchial asthma. *Br. med. J.*, **1**, 637-639.

Inhibition of constrictor responses of the rabbit ear artery by a mixture of oxytetracycline and ascorbic acid

D.A. McCULLOUGH & W.F.M. WALLACE
(introduced by I.C. RODDIE)

Department of Physiology, The Queen's University of Belfast, Medical Biology Centre, 97, Lisburn Road, Belfast BT9 7BL

Powis (1973) reported marked potentiation of constrictor responses of the isolated perfused rabbit ear artery by oxytetracycline, 10^{-4} mol/l. In attempting to confirm this finding, a brand of oxytetracycline was used which consists of a mixture of oxytetracycline and ascorbic acid powder. When this is made up to a solution containing oxytetracycline 10^{-4} mol/l, ascorbic acid is present at a concentration of 1.3×10^{-3} mol/l. Addition of this mixture to the perfusing fluid of the artery had no appreciable effect on its pH, but caused a progressive and marked reduction in responses to noradrenaline so that after 30 min perfusion average responses (rise in perfusion pressure) in six experiments to 5, 10 and 20 ng of noradrenaline were reduced from 25 ± standard error 3 to 11 ± 3, from 40 ± 6 to 15 ± 3 and from 57 ± 9 to 23 ± 6 mm Hg respectively. ($P < 0.01$ – paired t test – in each case) – Figure 1. Addition of the oxytetracycline alone caused a small, non-significant increase in responses (Figure 1).

In a further series of six experiments, ascorbic acid alone at a concentration of 1.1×10^{-3} mol/l caused only slight reduction of responses to noradrenaline. Responses to 5, 10 and 20 ng of noradrenaline were reduced from 29 ± 6 to 25 ± 5 ($P < 0.05$), from 42 ± 8 to 37 ± 7 ($P < 0.02$) and from 60 ± 13 to 53 ± 11 mm Hg ($P > 0.05$) after 30 min perfusion.

Constrictor responses to histamine (0.5, 1.0, 2.0 μg) showed a similar marked depression in the presence of the mixture of oxytetracycline and ascorbic acid. This depressant action of the mixture on arterial constrictor responses appears to be another example of the unexpected effects of tetracyclines when mixed with stabilizing agents (Sulkowski & Haserick, 1964).

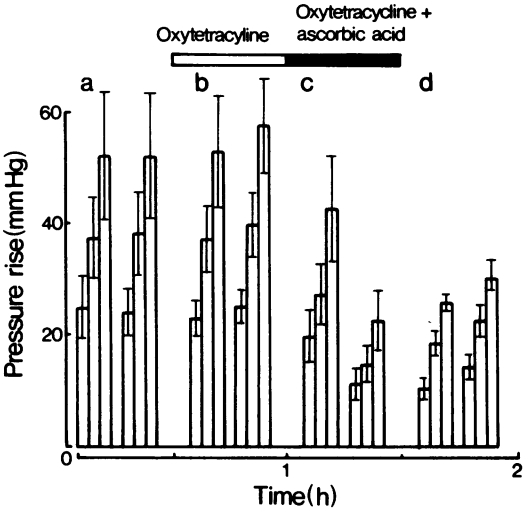

Figure 1 Effect on responses (rise in perfusion pressure) to noradrenaline of oxytetracycline, 10^{-4} mol/l and oxytetracycline 10^{-4} mol/l plus ascorbic acid 1.1×10^{-3} mol/l in the perfusate. Graded responses to noradrenaline, 5, 10 and 20 ng are shown. Results are means with standard errors from six experiments: (a) under control conditions, (b) with oxytetracycline present, (c) with the mixture present and (d) after a return to the control perfusate.

We would like to thank Mr R.G.P. Watson for helping with some of the experiments and Pfizer Ltd. for supplying oxytetracycline.

References

POWIS, G. (1973). Binding of catecholamines to connective tissue and the effect upon the responses of blood vessels to noradrenaline and to nerve stimulation. *J. Physiol., Lond.*, **234**, 145-162.

SULKOWSKI, S.R. & HASERICK, J.R. (1964). Simulated systemic lupus erythematosus from degraded tetracycline. *J. Am. med. Ass.*, **189**, 152-154.

Adrenergic blockade and the pulmonary pressor response to lactic acid

W.R.L. JAMES & A.J. THOMAS* (introduced by J.D.P. GRAHAM)

Experimental Laboratory, Sully Hospital and University Hospital of Wales, Cardiff

Vasoconstriction in the lung is an important protective response. Its mechanism in relation to drugs and hypoxia has been studied by others.

We find that the pulmonary vascular bed in the sheep responds to small doses of 4 ml 0.75 molar lactic acid with a 50% or greater increase in mean pulmonary artery pressure ($P\bar{p}a$). The lactic acid is injected into the jugular vein (J.V.) and the response follows in nine seconds. The $P\bar{p}a$ returns to near the previous level in four minutes. The test can be repeated many times provided sodium bicarbonate is given to maintain blood pH at or above 7.3. The sheep are anaesthetized with halothane and ventilated. Pressures are recorded continuously from the pulmonary artery and left ventricle.

Previous experiments have shown that the rise in Ppa is not due to an increase in flow or elevation of left atrial pressure but the change in Ppa reflects a change in pulmonary vascular resistance. It is of interest that lactic acid is a vasoconstrictor in the pulmonary vascular bed and a vasodilator in the skeletal muscular bed.

The injection of 10 mg phentolamine into the J.V. results 5 to 10 min later in marked reduction or abolition of the response to lactic acid.

Infusion of phenoxybenzamine, 30 mg in 200 ml of saline in 30 min, results 75 min later in the disappearance of the pressor response to lactic acid.

Reserpine 2.5 mg prevented the response after a variable time of the order of two hours. Atropine (12-17 mg) had no effect on the response.

Thus α-adrenoceptor blockade prevents the expected increase in $P\bar{p}a$ on injection of lactic acid and the effect of reserpine suggests that catecholamines play a part in the response.

Isoprenaline infusion (2 to 4 μg doses in 1 to 2 min), sufficient to raise the heart rate 40 beats per min, immediately abolishes the $P\bar{p}a$ response to lactic acid. We find, like others, that β-adrenoceptor blockade restores some of the pressor response removed by α-adrenoceptor blockade.

Several workers (Barer & McCurnie, 1969; Hyman, Woolverton, Guth & Ichinose, 1971) have demonstrated a pulmonary pressor response to various acids and the common factor is the hydrogen ion. Alpha adrenoceptors are particularly concerned in the response but the part played by β-adrenoceptors has yet to be determined. The consistent delay of 9 to 11 s in the appearance of the response remains unexplained.

References

BARRER, G.R. & McCURRIE, J.R. (1969). Pulmonary vasomotor responses in the cat: The effects and interrelationships of drugs, hypoxia and hypercopnia. *Q. Jl. exp. Physiol.*, **54**, 156-172.

HYMAN, A.L., WOOLVERTON, W.D., GUTH, P.S. & ICHINOSE, H. (1971). The pulmonary vasopressor response to decreases in blood pH in intact dogs. *J. clin. Invest.*, **50**, 1028-1043.