PROSTAGLANDINS AND ASTHMA

The possibility that the prostaglandins have a physiological or a pathological rôle in the control of bronchial muscle tone was first postulated when it was found that both E and F series prostaglandins have marked activity on isolated smooth muscle preparations. Thus prostaglandin $F_{2\alpha}$ ($\text{PGF}_{2\alpha}$) causes contraction of respiratory smooth muscle from a number of species (Anggard & Bergstrom, 1963) while prostaglandin E_1 (PGE_1) causes relaxation (Main, 1964). It is interesting that the relaxation due to the E prostaglandins can only be demonstrated in the presence of intrinsic tone or after contraction has been induced by acetylcholine or histamine. The A prostaglandins have a weaker relaxant effect than the E compounds but a longer duration of action (Horton & Jones, 1969) possibly because they are metabolized less rapidly in the lungs.

Human isolated bronchial muscle has intrinsic tone and $\text{PGF}_{2\alpha}$ has been shown to cause contraction and PGE_2 to cause relaxation (Sweatman & Collier, 1968). These effects are independent of vagal innervation or histamine release and are not affected by adrenoceptor blocking agents. Present evidence suggests that the prostaglandins act directly on smooth muscle although the E and A prostaglandins may induce relaxation by activating adenylcyclase and increasing intracellular cyclic AMP.

Studies in anaesthetized animals have in general confirmed the findings in isolated tissues, $\text{PGF}_{2\alpha}$ increasing bronchial resistance while PGE_1 antagonizes the increases in bronchial resistance due to histamine or vagal stimulation and sometimes reduces resting tone (Main, 1964). Rosenthale, Dervinis, Begany, Lapidus & Gluckman (1970) and Rosenthale, Dervinis & Kassarch (1971) have shown that both PGE_1 and PGE_2 by aerosol can prevent the bronchoconstriction produced by histamine or anaphylaxis although there is considerable species variation; for example, PGE_2 is a relatively ineffective bronchodilator in the dog while in the monkey both PGE_1 and PGE_2 are approximately 20 times more potent than isoprenaline.

In an interesting comparative study in the guinea-pig (Large, Leswell & Maxwell, 1969), PGE_1 and isoprenaline had similar bronchodilator activity when given intravenously, but when given by aerosol, PGE_1 had 10-100 times the activity of isoprenaline. The duration of bronchodilator activity was similar for both agents and in contrast to isoprenaline, PGE_1 by aerosol did not produce

tachycardia and its activity was not blocked by propranolol.

The difference in the activity of PGE_1 by the i.v. and aerosol route may be due to the fact the infused prostaglandins are rapidly inactivated by the lungs. Prostaglandins of the E, F and A series are stable in the blood (Ferreira & Vane, 1967) but their half-life in the circulation is short because 90-95% of $\text{PGF}_{2\alpha}$, PGE_1 and PGE_2 are metabolized in one passage through the pulmonary circulation in a variety of animal species; the A prostaglandins appear to be inactivated less rapidly (Piper, Vane & Wyllie, 1970). Similar inactivation of prostaglandins may occur in the human lung.

Initial studies with freon-activated aerosol preparations of the E prostaglandins were performed to investigate their potential as therapeutic agents. Using simple spirometry and measuring the forced expiratory volume in one second (FEV_1) it was found that the inhalation of PGE_1 ($55\mu\text{g}$ triethanolamine salt) produced bronchodilatation in asthmatics comparable in degree and duration to that of isoprenaline ($550\mu\text{g}$) (Cuthbert, 1969). However, inhalation of the free acid of PGE_1 caused irritation of the upper respiratory tract, coughing and retrosternal soreness in healthy subjects. Although these effects were less marked when PGE_1 was inhaled as its neutral triethanolamine salt in both healthy and asthmatic subjects, one asthmatic did develop bronchospasm over 1 h which was almost certainly reflexly induced by the coughing and clearing of the throat following the PGE_1 inhalation (Cuthbert, 1969).

Using total body plethysmography, a comparison has been made between the effects of aerosol of the triethanolamine salts of PGE_1 and PGE_2 , and isoprenaline sulphate on bronchial muscle tone in healthy and asthmatic subjects (Smith & Cuthbert, 1973). In both groups PGE_1 and PGE_2 were effective bronchodilators causing a fall in airways resistance and a rise in specific airways conductance. The bronchodilator effects of both PGE_1 and PGE_2 ($55\mu\text{g}$) were comparable with those of isoprenaline ($550\mu\text{g}$) in both degree and duration although these changes were more marked in the asthmatics.

Despite their promising bronchodilator properties it seems unlikely that any naturally-occurring prostaglandin will prove to be of value as a bronchodilator aerosol in the treatment of asthma. There are two main reasons for this statement. Firstly, all the prostaglandin aerosols so far tested

cause irritation of the upper respiratory tract; it is not yet known whether this is a property common to all prostaglandins. Secondly, the E prostaglandins are unstable in solution which poses problems in any proposed aerosol preparation. It is possible that these difficulties might be overcome by the synthesis of potent stable prostaglandin analogues. Intravenous PGE₂ is also unlikely to have any therapeutic application since it is not a very effective bronchodilator in asthmatics and gives rise to troublesome adverse effects (Smith, 1974).

Prostaglandin F_{2α} (PGF_{2α}) has been shown to be a potent bronchoconstrictor when inhaled by healthy subjects (Hedqvist, Holmgren & Mathé, 1971; Smith & Cuthbert, 1972), which is of short duration and can be effectively reversed by both isoprenaline or PGE₂ inhalation. PGF_{2α} inhalation has similar irritant effects to those noted with the E series prostaglandins. Pretreatment of the subjects with several possible antagonists including flufenamic acid, atropine and disodium cromoglycate failed to modify the bronchoconstrictor effect of PGF_{2α} inhalation (Smith, Cuthbert & Dunlop, 1975).

Mathé, Hedqvist, Holmgren & Svanborg (1973) have drawn attention to the possible role of PGF_{2α} in the aetiology of bronchial asthma. Using total body plethysmography, dose response curves for the bronchoconstrictor effects of histamine and PGF_{2α} were constructed in healthy and asthmatic subjects. Asthmatics were found to be about 10 times more sensitive than healthy subjects to histamine inhalation but about 8000 times more sensitive than healthy subjects to PGF_{2α} inhalation. The authors suggested that hypersensitivity to endogenous PGF_{2α} may significantly contribute to increased airways resistance and that the local release of PGF_{2α} might explain the precipitation of the asthmatic attack by a wide variety of stimuli. A recent study (Smith, Cuthbert & Dunlop, 1975) has confirmed the hypersensitivity of asthmatics to PGF_{2α} inhalation but has shown a very marked individual variation, some asthmatics being no more sensitive than healthy subjects while others showed a similar hypersensitivity to that reported by Mathé *et al.* (1973). This variation in sensitivity was not correlated with any particular feature of the nature or duration of the asthma or its treatment.

Prostaglandins of the E and F series are normally present in animal and human lungs (Anggard, 1965; Karim, Sandler & Williams, 1967) and are known to be released by a variety of stimuli (Piper & Vane, 1971) including anaphylaxis, embolization, mechanical stimulation, infusion of histamine or 5-HT and by inflation. It seems probable that the common

factor for release is disturbance of the cell membrane (Piper & Vane, 1971). Although these findings and the hypersensitivity of some asthmatics to PGF_{2α} have given rise to considerable speculation on the role of the prostaglandins in allergic bronchospasm in man, on available evidence it would seem more likely that the release of prostaglandins under these conditions is a secondary phenomenon rather than being primarily responsible for allergic bronchospasm.

The discovery that the non-steroidal anti-inflammatory drugs, for example, indomethacin, aspirin and salicylate, are effective inhibitors of the synthesis of both E and F prostaglandins (Vane, 1971) has led to some experiments to attempt to determine the role of the prostaglandins in the maintenance of bronchial smooth muscle tone. Indomethacin certainly is markedly effective in reducing the tone of isolated preparations of guinea-pig and human bronchial muscle (Farmer, Farrar & Wilson, 1974; Dunlop & Smith, 1975) but it is not certain whether these effects are due to the inhibition of prostaglandin synthesis or antagonism of the effects of endogenous PGF_{2α} and whether such results can be extrapolated to the asthmatic subject. To investigate this possibility, a clinical trial is reported by Smith (1975) on p. 307 of this issue. In a dosage of 200 mg a day, indomethacin failed to produce any improvement in exercise-induced bronchospasm, antigen challenge or measurement of peak flow rate in asthmatic subjects. Since this dose of indomethacin is known to reduce the urinary excretion of prostaglandin metabolites in man almost completely (Samuelsson, 1973) and that PGF_{2α} metabolites appear in the blood following antigen challenge in asthmatics (Gréen, Hedqvist & Svanborg, 1974) these results are interpreted as throwing considerable doubt on the hypothesis that the prostaglandins are important mediators in asthma.

This interpretation is attractive especially since some asthmatics are known to be extremely sensitive to inhaled PGF_{2α} but it does depend on certain assumptions. Firstly, that doses of indomethacin which inhibit the urinary excretion of prostaglandin metabolites also significantly reduce the biosynthesis of prostaglandins in the lungs. Secondly, since indomethacin inhibits the biosynthesis of both E and F prostaglandins it is assumed that the effect of a reduction in the bronchoconstrictor PGF_{2α} is not simply offset or otherwise influenced by a comparable reduction in the bronchodilator PGE₂. It is true that E prostaglandins can occasionally cause bronchoconstriction (Cuthbert, 1969; Mathé *et al.*, 1973) but this problem will probably not be resolved

until specific inhibitors of the synthesis or action of the F prostaglandins are developed. The availability of such compounds will also resolve the important question whether a specific reduction or antagonism of $\text{PGF}_{2\alpha}$ will prove of value in the treatment of asthma.

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