Prostaglandin levels in blood plasma during asthmatic attacks in patients with aspirin idiosyncrasy

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Summary

It has been suggested that prostaglandin release is an important factor in the pathogenesis of bronchial asthma. Aspirin inhibits prostaglandin synthesis, yet there are a group of patients, with aspirin idiosyncrasy, who develop asthma after ingestion of aspirin. We measured prostaglandin levels in seven individuals with this syndrome. Only trace amounts of PGE₂ and PGF_{2α} were found in plasma during asthmatic attacks provoked by aspirin.

Introduction

Prostaglandins E₂ and F_{2α} are normally present in the human lung and bronchi (Anggård, 1965; Karim, Sandler and Williams, 1967). Prostaglandin F_{2α} (PGF_{2α}) is released from the lungs of guinea-pigs and rats during anaphylactic reactions (Piper and Vane, 1969), and in man it contracts bronchial smooth muscle *in vitro* and *in vivo* (Sweatman and Collier, 1968; Smith and Cuthbert, 1972). Asthmatic patients appear to be remarkably sensitive to inhaled PGF_{2α} (Mathé *et al.*, 1973), and it may be that endogenous PGF_{2α} plays a significant role in the pathogenesis of bronchial asthma.

Aspirin and indomethacin strongly inhibit prostaglandin synthesis (Vane, 1971; Smith and Willis, 1971) and it has been suggested that, thereby, aspirin has a bronchodilator action.

A group of asthmatics, however, appear to be sensitive to aspirin and develop increased airways obstruction within minutes of aspirin ingestion (Samter and Beers, 1967). This response appears to be a chemically mediated rather than an immunological one, as other analgesics, structurally unrelated to aspirin, have similar effects on these individuals (Smith, 1971). The chemical mediator may well be PGF_{2α}.

In order to determine if asthmatic attacks occurring in this syndrome were associated with a rise in the prostaglandin levels, we measured PGE₂ and PGF_{2α} levels in the plasma of seven patients during asthmatic attacks precipitated by oral challenge with soluble aspirin.

Method

Seven patients with aspirin-induced asthma were studied. Previously, these patients had been found, after aspirin ingestion, to have airways obstruction demonstrated by changes in the pulmonary function tests, but subjectively they had been unaware of severe dyspnoea. Clinical features of these patients are outlined in Table 1.

No changes were made in their normal medication.

The FEV₁% was calculated from measurements of the forced vital capacity (FVC), and forced expiratory volume in one second (FEV₁). The maximum breathing capacity (MBC) was also measured. These pulmonary function tests (PFTs) were performed at zero time and at 30-min intervals for 2 hr.

In four patients blood was taken for measurement of PGE₂ and PGF_{2α} levels immediately before the PFTs at zero time.

Soluble aspirin was given to each of the seven patients after the completion of the PFTs at zero time. The dose, varying between 80 mg and 600 mg, depended on their previous response to aspirin ingestion.

Airways obstruction invariably occurred at 60 min with a fall in the FEV₁% and MBC. At this time blood was taken for prostaglandin measurements in all seven patients.

In each case blood was taken from an antecubital vein, via a BD 'Vacutainer'® system into lithium heparin tubes. The samples were centrifuged

TABLE 1. Clinical features of seven subjects with aspirin-induced asthma

Patient	Sex	Age	Duration of asthma (years)	Nasal polypi (years)	Skin tests	Other drug sensitivities	Medication
S.T.	M	24	6	2	House dust* Moulds*	Nil	Daneral S.A.
S.T.	F	23	2/3	—	—	Indomethacin → asthma	Nil
L.W.	M	50	3	—	—	Nil	DSCG† Tedral S.A.
L.K.	F	41	11	14	—	Nil	Prednisolone 10 mg/day
E.S.	F	38	2	15	—	Paracetamol → asthma	Prednisolone 2 mg/day Beclomethasone inhaler
M.C.	F	32	9	4	—	Paracetamol → asthma	Salbutamol
S.L.	F	29	6	5	Feathers* Moulds*	Nil	DSCG† Prednisolone 5 mg/day Beclomethasone inhaler

* Mild reaction.

† DSCG = Disodium cromoglycate.

without delay to prepare plasma. A 5 ml sample of plasma was added to 2 ml ethanol to help preserve the prostaglandins before their extraction.

Technique of analysis

The prostaglandins were extracted essentially as described by Unger, Stamford and Bennett (1971) and separated into PGF and PGE fractions on silicic acid columns (Zusman, Caldwell and Speroff, 1972). The PGE content was determined by bioassay on the rat stomach strip (Silver *et al.*, 1972), and the PGF_{2α} content by radioimmunoassay using an antiserum generated against a PGF_{2α} albumin conjugate (Caldwell *et al.*, 1971).

Results

The changes in the PFTs in response to aspirin ingestion are outlined in Table 2.

The levels of plasma PGE₂ were less than 350 pg/ml, and the levels of plasma PGF_{2α} were less

than 175 pg/ml in all the samples studied. In other words, the levels of PGE₂ and PGF_{2α} were not raised.

Discussion

It has been suggested that prostaglandin release may play a significant role in the pathogenesis of bronchial asthma (Mathé *et al.*, 1973). Aspirin ingestion in aspirin-sensitive individuals provokes severe asthmatic attacks and would be expected, therefore, to be associated with raised levels of PGF_{2α}. However, from our results, it would appear that only trace amounts of PGE₂ and PGF_{2α} are present in the circulation during such attacks, and that some other mechanism is responsible for the production of asthma in these individuals.

On the other hand, these results are insufficient to disprove the hypothesis of Mathé *et al.* (1973) that release of PGF_{2α} from lung tissue plays a significant part in bronchial asthma. Firstly, in some of the

TABLE 2. Changes in pulmonary function tests after aspirin ingestion in seven subjects with aspirin idiosyncrasy

Patient	Sex	FEV percentage		MBC litres/min		Aspirin dose (mg)	Sample taken for measurements of prostaglandin levels	
		0 min	60 min	0 min	60 min		0 min	60 min
S.T.	M	76	56	152	58	300	Yes	Yes
S.T.	F	94	74	110	66	300	Yes	Yes
L.W.	M	46	40	66	52	300	Yes	Yes
L.K.	F	77	67	70	68	600	Yes	Yes
E.S.	F	80	72	113	98	600	No	Yes
M.C.	F	65	56	65	58	81	No	Yes
S.L.	F	46	42	64	54	81	No	Yes

patients examined by these authors, as little as 5–6 pmol $\text{PGF}_{2\alpha}$ produced broncho-constriction. If as little as this was produced by the lungs, it would be impossible to detect an increase in plasma $\text{PGF}_{2\alpha}$ by our present methods (sensitivity 0.5 pmol/ml plasma). Secondly, in some patients, $\text{PGF}_{2\alpha}$ inhaled at zero time produced an effect which lasted for 1 hr. Since this $\text{PGF}_{2\alpha}$ may be metabolized very rapidly, the broncho-constrictor effect could persist longer than the prostaglandin. Smith and Cuthbert (1971) have demonstrated a delay in the onset of the broncho-constrictor effect of $\text{PGF}_{2\alpha}$ in healthy volunteers, suggesting that this prostaglandin may itself be releasing another broncho-constrictor agent, or possibly undergoing metabolism to a more active substance.

In order to be certain that there is not a short-lived increase in plasma $\text{PGF}_{2\alpha}$ during an asthmatic attack, time-course measurements of $\text{PGF}_{2\alpha}$ levels should be done using a continuous sampling technique. It would also be of value to measure the levels of 9,11-dihydroxy-15 ketoprost-5-enoic acid, the major metabolite of $\text{PGF}_{2\alpha}$ (Beguín *et al.*, 1972).

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