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 PGE$_2$ and PGF$_{2\alpha}$ were found in plasma during asthmatic attacks provoked by aspirin.

Introduction
Prostaglandins E$_2$ and F$_{2\alpha}$ are normally present in the human lung and bronchi (Anggard, 1965; Karim, Sandler and Williams, 1967). Prostaglandin F$_{2\alpha}$ (PGF$_{2\alpha}$) 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$_{2\alpha}$ (Mathé et al., 1973), and it may be that endogenous PGF$_{2\alpha}$ 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$_{2\alpha}$.

In order to determine if asthmatic attacks occurring in this syndrome were associated with a rise in the prostaglandin levels, we measured PGE$_2$ and PGF$_{2\alpha}$ 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 FEV$_1$% was calculated from measurements of the forced vital capacity (FVC), and forced expiratory volume in one second (FEV$_1$). 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 PGE$_2$ and PGF$_{2\alpha}$ 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 FEV$_1$% and MBC. At this time blood was taken for prostaglandin measurements in all seven patients.

In each case blood was taken from an ante-cubital 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

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

* 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 PGE<sub>2α</sub> content by radioimmunoassay using an antiserum generated against a PGF<sub>2α</sub> 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 PGE<sub>2</sub> were less than 350 pg/ml, and the levels of plasma PGE<sub>2α</sub> were less than 175 pg/ml in all the samples studied. In other words, the levels of PGE<sub>2</sub> and PGE<sub>2α</sub> 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 PGE<sub>2α</sub>. However, from our results, it would appear that only trace amounts of PGE<sub>2</sub> and PGE<sub>2α</sub> 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 PGE<sub>2α</sub> from lung tissue plays a significant part in bronchial asthma. Firstly, in some of the

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>FEV percentage 0 min</th>
<th>FEV percentage 60 min</th>
<th>MBC litres/min 0 min</th>
<th>MBC litres/min 60 min</th>
<th>Aspirin dose (mg)</th>
<th>Sample taken for measurements of prostaglandin levels 0 min</th>
<th>Sample taken for measurements of prostaglandin levels 60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.T.</td>
<td>M</td>
<td>76</td>
<td>56</td>
<td>152</td>
<td>58</td>
<td>300</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>S.T.</td>
<td>F</td>
<td>94</td>
<td>74</td>
<td>110</td>
<td>66</td>
<td>300</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>L.W.</td>
<td>M</td>
<td>46</td>
<td>40</td>
<td>66</td>
<td>52</td>
<td>300</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>L.K.</td>
<td>F</td>
<td>77</td>
<td>67</td>
<td>70</td>
<td>68</td>
<td>600</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>E.S.</td>
<td>F</td>
<td>80</td>
<td>72</td>
<td>113</td>
<td>98</td>
<td>600</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>M.C.</td>
<td>F</td>
<td>65</td>
<td>56</td>
<td>65</td>
<td>58</td>
<td>81</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>S.L.</td>
<td>F</td>
<td>46</td>
<td>42</td>
<td>64</td>
<td>54</td>
<td>81</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
patients examined by these authors, as little as 5–6 pmol PGE$_{2a}$ produced broncho-constriction. If as little as this was produced by the lungs, it would be impossible to detect an increase in plasma PGE$_{2a}$ by our present methods (sensitivity 0.5 pmol/ml plasma). Secondly, in some patients, PGE$_{2a}$ inhaled at zero time produced an effect which lasted for 1 hr. Since this PGE$_{2a}$ 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 PGE$_{2a}$ 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 PGE$_{2a}$ during an asthmatic attack, time-course measurements of PGE$_{2a}$ 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-enonic acid, the major metabolite of PGE$_{2a}$ (Beguin et al., 1972).

References


