EFFECT OF LEUKOTRIENES C₄ AND D₄ ON PROSTAGLANDIN I₂-LIBERATION FROM HUMAN LYMPHATICS

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ABSTRACT

Whereas prostaglandin I₂ (PGI₂), a major metabolite of human lymphatics, does not itself affect lymphatic contractility significantly, it is able to counterbalance the contractile response to thromboxane and leukotrienes. We now demonstrate that leukotrienes C₄ and D₄ evoke a dose-dependent increased production of PGI₂ from human lymphatics. It is likely that leukotrienes either exert a contractile rhythmic effect on human lymphatics or, alternatively, evoke increased PGI₂-formation which relaxes human lymphatics. These mechanisms may be of local importance in regulating lymphatic “tone” at sites of inflammation as leukotrienes are liberated from activated white blood cells.

Rhythmic contraction of human lymphatics has been recognized for centuries (1) and is now considered a major factor in lymph propulsion (2). Olsszewski and Engeset (3) first pointed out that prostaglandin F₂α-induced contraction of lymphatics. Later Johnston et al (4,5) observed that thromboxane A₂ stimulated lymphatics to contract and leukotrienes exerted a rhythmic contraction of lymphatics. These findings, in conjunction with evidence that various prostaglandins are found in the effluent of lymph (6-8), raised the question whether stimulation of PGI₂-synthesis by leukotrienes C₄ and D₄ (7,8) occurred in human lymphatics, and whether contraction of lymphatics was rhythmically coregulated by these eicosanoids (4,9).

MATERIALS AND METHODS

We studied three human lymphatics (obtained during lymphangiography after informed consent) from two males and one female aged 15-41 years. These lymph vessels were cut into rings with a circumference of approximately 0.5 cm. Two wires were fixed to the lumen as described by Johnston and Gordon (10), the lower one fixed to the bottom of a 5 ml perfusion bath, the upper one connected with an isometric transducer (Harvard Instruments recorder Pharmacia). Lymphatics were constantly perfused with an oxygenated (95% O₂, 5% CO₂) Krebs-Ringer solution at a constant temperature of 37°C. Thereafter, the lymphatics were placed under 0.5g. The leukotriene was added in concentrations of 2x10⁻⁸, 2x10⁻⁹, 2x10⁻¹⁰.

From five lymph vessels of three males and two females in the age range of 16-47 years PGI₂-formation (1) was bioassayed. Briefly, tissue samples were incubated at 22°C for three minutes in Tris HCL buffer (pH 7.4). After incubation, 100 μl of the incubation buffer were removed and added to a platelet rich-plasma. Platelet-rich plasma was prepared after anticoagulation with 3.8% sodium citrate and adjusted to a con-
stant platelet count of 250x10^9/μl. In the prewarmed aggregometer one minute later aggregation was induced by ADP (100 μl, 1μmol). The inhibitory activity of the incubation buffer was quantified using a synthetic PGI2 standard. Together with the tissue samples the leukotrienes C4 and D4 were incubated in a dose range from one to 100 ng/ml. Prostacyclin formation is shown in pg/mg/min.

STATISTICS

Values are shown as mean ± SD; calculation for significance was done using Student's t-test.

RESULTS

Leukotriene C4 caused a rhythmic contraction of human lymph vessels (Fig. 1). Leukotrienes C4 and D4 promoted a dose-dependent increase in prostaglandin I2-formation by human lymphatics reaching the level of significance at doses >50ng/ml (Table 1).

DISCUSSION

Leukotrienes are formed predominantly by white blood cells (12) and induce a notable increase in prostaglandin I2-formation (7,8) via prostacyclin synthetase. Normally, human lymphatics are not able to synthesize leukotrienes (13), and it is likely that as part of the local inflammatory response white blood cells are the primary source of these eicosanoids. The double action of leukotrienes (i.e. either in-

<table>
<thead>
<tr>
<th>Amount</th>
<th>LTC4 (mean ± SD)</th>
<th>LTD4 (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>buffer</td>
<td>4.71±2.27</td>
<td>4.86±2.51</td>
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<tr>
<td>+ 1 ng</td>
<td>4.85±2.35</td>
<td>4.80±2.43</td>
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<tr>
<td>+ 5 ng</td>
<td>4.78±2.17</td>
<td>4.93±1.83</td>
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<td>+ 10 ng</td>
<td>5.56±2.29</td>
<td>5.17±1.96</td>
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<tr>
<td>+ 50 ng</td>
<td>7.63±2.71*</td>
<td>8.04±2.57*</td>
</tr>
<tr>
<td>+ 100 ng</td>
<td>10.84±2.16*</td>
<td>11.23±2.27*</td>
</tr>
</tbody>
</table>

* p < 0.01

Table 1.
Stimulation of PGJ2-synthesis by LTC4 and LTD4

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distribution of prostaglandins in afferent and efferent lymph from inflammatory sites. 

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specific total synthesis of a “slow reacting 
substance” of anaphylaxis, leucotriene C4. J 

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