Prostacyclin Synthesis in Human Lymphatics

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Summary
The ability of human lymphatics to generate prostacyclin in important amounts (4.5 ± 2.1 pg/mg/min) is described. The prostacyclin produced, exhibits the same properties as reported for arterial and venous tissue. No age and sex difference could be observed. The role of prostacyclin in physiology of lymphatics, however, is unknown.

Key-Words: Prostacyclin generation – Human lymphatics

Introduction
The original work by Moncada et al. (1) has demonstrated firstly that arterial endothelial cells generate prostacyclin (PGI₂), a newly discovered prostaglandin, with a very potent platelet aggregation inhibitory effect in vivo and in vitro. Later on it has been shown that venous endothelium is able to produce important amounts of PGI₂ too (2). Similar results were obtained with cultured endothelial cells (3). As to our knowledge, the question of PGI₂-synthesis of lymphatics has not yet been studied.

Aim of this study was to prove if the PGI₂-formation is a metabolic property of all endothelial cells or if this is limited to the endothelium of blood vessels only.

Material and Methods
We have investigated eight samples of human lymphatics from 3 males and 5 females aged between 15 and 56 years. The bioassayed tissue (mean tissue wet weight: 1.7 ± 0.8 mg) was controlled morphologically after fixation in 5% buffered glutaraldehyde before and after estimation of PGI₂-activity. 4 patients had morphologically normal lymphatics, 4 had an obliteratorative lymphangiopathy. As the lymphatic rings had a comparable wall thickness, the produced PGI₂-activity was expressed in terms of wet weight. The lymphatics removed after lymphangiography from the dorsal pedis region were incubated at 22°C for 3 minutes in tris-HCl buffer (0.05 mol/l; pH 7.5), Ketoprofen (200 µg/ml), a cyclooxygenase inhibitor (Fig. 2), angiotensin II (20 µg/ml) and 15-hydroxyperoxyarachidonic acid (15-HPAA), a specific inhibitor of prostacyclin synthetase as well as in platelet rich (PRP) and platelet poor plasma (PPP). 100 µl of the supernatant fraction were withdrawn and added to PRP (prepared by sedimentation and differential centrifugation of blood anticoagulated with 3.8% sodium citrate) one minute prior to induction of aggregation with ADP. Platelet aggregation was performed in a Born-type aggregometer with 0.7 ml PRP samples. The aggregation was induced by ADP in final concentrations of 1–2 µmol/l. The PGI₂-activity as expressed by the platelet aggregation inhibiting effect quantitatively by means of a synthetic PGI₂-standard (kindly supplied by Dr. John E. Pike, The Upjohn Company, Kalamazoo, Michigan, USA) in pg PGI₂/mg tissue wet weight/min. The tissue wet weight of the lymphatics was examined immediately after bioassay performance. The properties of PGI₂ were tested as described earlier (4, 5).

Results
Human lymphatics are able to generate PGI₂.
Table 1 Prostacyclin formation by human lymphatic and venous tissue in pg PG\textsubscript{1}2, and mean wet weight of the examined tissue

<table>
<thead>
<tr>
<th>human tissue</th>
<th>PG\textsubscript{1}2-formation (pg/mg tissue wet weight/min)</th>
<th>mean tissue wet weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lymphatics</td>
<td>4.5 ± 2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>veins</td>
<td>6.4 ± 2.3</td>
<td>9.0</td>
</tr>
</tbody>
</table>

\(\bar{x} \pm \text{SEM}\)

Fig. 1 Inhibition of an ADP-induced platelet aggregation curve; (1) buffer control, (2) 3 mg lymphatic tissue incubated in buffer for three minutes, (3) 3 mg lymphatic tissue incubated directly in PRP for three minutes, (4) 3 mg lymphatic tissue incubated in 15-HPAA. T . . . transmission

in amounts which are lower than human arterial and venous tissue (Table 1). The amounts synthetized (4.5 ± 2.1 pg PG\textsubscript{1}2/mg/min) are relatively high in comparison to vascular tissue of various species. No age and sex difference in PG\textsubscript{1}2-production could be detected. Incubation of the lymphatics in PRP directly (Figure 1) enhanced the PG\textsubscript{1}2-formation significantly. Incubation in ketoprofen and 15-HPAA (Figure 2) inhibited PG\textsubscript{1}2-generation completely,

whereas angiotensin II and PPP enhanced the PG\textsubscript{1}2-synthesis.

The platelet aggregation inhibiting agent was identified for it being PG\textsubscript{1}2 by its half life time, pH-dependent degradation, heat instability and specific inhibition by 15-HPAA. No difference in PG\textsubscript{1}2-synthesis between normal and pathologically altered lymphatics could be detected.

**Discussion**

These data confirm the view, that prostacyclin formation is an important metabolic property of all endothelial cells, also of human lymphatics, depending on the type of the vessel (6), localization (7) and species (8). However, the role in normal physiology of human lymphatics is unclear. Whereas the platelet aggregation inhibiting effect of PG\textsubscript{1}2 (9) in human lymphatics seems to be of no importance, the effect of PG\textsubscript{1}2 on cell contractility (10) might play an important role in lymph transport. Because of the small size of the vessels, the study of PG\textsubscript{1}2-activity in the different wall layers was not possible without any mechanical damage leading to liberation of enzymes (11) and elevated PG\textsubscript{1}2-levels. Therefore, the further examination of the role of PG\textsubscript{1}2 in lymphatics in pathophysiology will be extremely difficult because of methodological limitation (12).
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