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Prostacyclin Synthesis in Human Lymphatics

Eva Mannheimer, M.D., H. Sinzinger, M.D., R. Oppolzer, M.D., and K. Silberbauer, M.D.

Kardiologische Universitätsklinik (Vorstand: Prof. Dr. F. Kaindl), Atherosklerose-forschungsgruppe am Institut für Medizinische Physiologie (Vorstand: Prof. Dr. W. Auerswald), 1. Anatomische Lehrkanzel (Vorstand: Prof. Dr. H. Ferner) und II. Medizinische Universitätsklinik (Vorstand: Prof. Dr. G. Geyer), Wien, Österreich

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 (PGI_2), 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 PGI_2 too (2). Similar results were obtained with cultured endothelial cells (3). As to our knowledge, the question of PGI_2-synthesis of lymphatics has not yet been studied.

Aim of this study was to proove if the PGI_2-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 PGI_2-activity. 4 patients had morphologically normal lymphatics, 4 had an obliterative lymphangiopathy. As the lymphatic rings had a comparable wall thickness, the produced PGI_2-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-hydroxy-peroxyarachidonic 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 PGI_2-activity as expressed by the platelet aggregation inhibiting effect quantitatively by means of a synthetic PGI_2-standard (kindly supplied by Dr. *John E. Pike,* The Upjohn Company, Kalamazoo, Michigan, USA) in pg PGI_2/mg tissue wet weight/min. The tissue wet weight of the lymphatics was examined immediately after bioassay performation. The properties of PGI_2 were tested as described earlier (4, 5).

Results

Human lymphatics are able to generate PGI_2

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Table 1 Prostacyclin formation by human lymphatic and venous tissue in pg PGI_2, and mean wet weight of the examined tissue

human tissue	PGI_2-formation (pg/mg tissue wet weight/min)	mean tissue wet weight (mg)
lymphatics	4.5 ± 2.1	1.7
veins	6.4 ± 2.3	9.0

$\bar{x}$ ± SEM

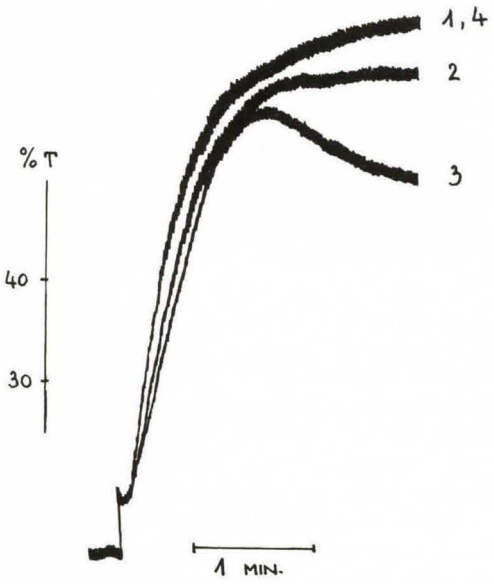

Fig. 1 Inhibition of an ADP-induced platelet aggregation curve; (1) buffer control, (2) 3 mg lymphatic tissue incubated in buffer for three minutes, (3) 3 mg lymphatic tissue incubated directly in PRP for three minutes, (4) 3 mg lymphatic tissue incubated in 15-HPAA. T . . . transmission

in amounts which are lower than human arterial and venous tissue (Table 1). The amounts synthetized (4.5 ± 2.1 pg PGI_2/mg/min) are relatively high in comparison to vascular tissue of various species. No age and sex difference in PGI_2-production could be detected. Incubation of the lymphatics in PRP directly (Figure 1) enhanced the PGI_2-formation significantly. Incubation in ketoprofen and 15-HPAA (Figure 2) inhibited PGI_2-generation completely,

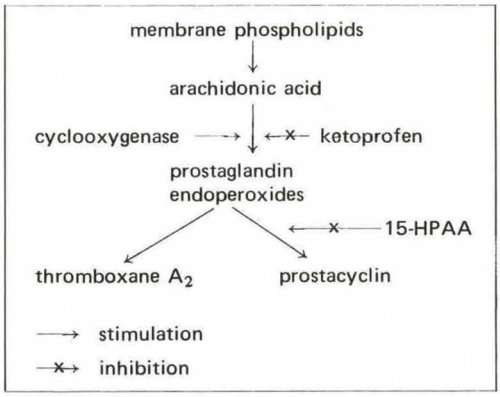

Fig. 2 Scheme of the present knowledge of prostaglandin metabolism and the inhibiting agents (15-HPAA, Ketoprofen) used

whereas angiotensin II and PPP enhanced the PGI_2-synthesis.

The platelet aggregation inhibiting agent was identified for it being PGI_2 by its half life time, pH-dependent degradation, heat instability and specific inhibition by 15-HPAA. No difference in PGI_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 PGI_2 (9) in human lymphatics seems to be of no importance, the effect of PGI_2 on cell contractility (10) might play an important role in lymph transport. Because of the small size of the vessels, the study of PGI_2-activity in the different wall layers was not possible without any mechanical damage leading to liberation of enzymes (11) and elevated PGI_2-levels. Therefore, the further examination of the role of PGI_2 in lymphatics in pathophysiology will be extremely difficult because of methodological limitation (12).

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Prof. Eva Mannheimer, M.D., Department of Cardiology, A-1090 Vienna, Garnisongasse 13, Austria
H. Sinzinger, M.D., Atherosclerosis Research Group at the Department of Medical Physiology, A-1090 Vienna, Schwarzspanierstr. 17, Austria