Prostaglandins and Other Eicosanoids in the Cardiovascular System

Editor
K. Schrör, Köln

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Nürnberg-Fürth, May 9–11, 1984

Prostaglandins and Other Eicosanoids in the Cardiovascular System

Experimental Data – Clinical Experience

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Preface

This volume contains the communications from a Symposion on Prostaglandins and other Eicosanoids in the Cardiovascular System held in Nürnberg-Fürth on May 9–11, 1984.

The Conference was organized to bring clinicians, basic scientists and other individuals not yet intimately involved in the eicosanoid area together for three days of concentrated discussions on mechanistic and therapeutic approaches to eicosanoids in the cardiovascular system. The current knowledge on this issue with particular reference to possible clinical use was critically summarized in lectures given by invited well-known experts. These reviews were communicated by a number of specific experimental and clinical presentations. Furthermore, there were two podium discussions on concepts, methods and possible pitfalls in eicosanoid sampling and assay procedures. The about 300 participants came from many different countries in America, Asia, Europe and from New Zealand. Partly reflecting to this diversity, the editing policy has been to remove ambiguities without attempting to improve a completely uniform style.

The success of the Conference was made possible by the efforts of many engaged subjects and organizations. The organizers are particularly grateful to the chairmen and speakers. It is a great pleasure to acknowledge the generous financial and technical support provided by Schering AG West Germany allowing the publication of the abstracts and proceedings, and Sanol-Schwarz GmbH (Monheim, FRG) for arranging the meeting and all of the social events around. Considerable financial support was also provided by Albert-Roussel Pharma GmbH (Wiesbaden, FRG), Laevosan Pharmaceuticals (Linz, Austria) and Dr. Willmar Schwabe Arz-

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Prostaglandins and Other Eicosanoids in the Cardiovascular System

Editorial

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Introduction

The history of "prostaglandin(s)" starts with the detection of a smooth muscle relaxing and blood pressure lowering activity in human seminal plasma by *von Euler* in 1934 and was collaborated by the finding that acidic lipids are responsible for these reactions. During the following 50 years many of these acidic lipids have been isolated that are formed via the so-called "arachidonic acid cascade", and their number still continuously tends to increase. Again, some of these derivatives, most notably prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), have been detected because of biological actions on blood platelets and vessel tone. Together with PGE_2, leukotrienes (LT's) and a number of other hydroperoxy and hydroxy fatty acids, commonly referred to as eicosanoids, they have profound activities on a variety of cardiovascular preparations, including changes in vascular permeability and vasomotor actions. This editorial summarizes and comments some of the data reported on this issue during the Symposion with particular emphasis to current and future clinical implications.

Formation and Action of Eicosanoids in the Cardiovascular System

Platelets, leukocytes, endothelial and smooth muscle cells are not only major sites of eicosanoid formation in the cardiovascular system but also major targets for eicosanoid action. This raises the question of the

biological significance of the eicosanoid system for cardiovascular homeostasis. Eicosanoids may be considered as a membrane-related defense mechanism. The system appears to be controlled by the availability of free precursor fatty acids, most notably arachidonic acid. Once the free precursor is available, it can be transformed into several products by the same cell(s) in the environment. This seems to be primarily a local event which is limited to the site of formation.

As reviewed by Dr. *Vane* (Beckenham), it seems that in diseases where there is a tendency for thrombosis to develop, thromboxane A_2 production is increased or PGI_2 production reduced, or both, whilst the opposite is found in some diseases associated with increased bleeding time. Thus, imbalances may exist between thromboxane and prostacyclin. This is probably of less importance under baseline conditions but may become significant under conditions of stimulation. Thus, a tentatively synergistic action between two different principles may become converted into a pathophysiologically relevant disturbance of homeostasis.

The current knowledge on eicosanoid metabolism and actions in man was summarized in review lectures given by Dr. *Kaijser* (Stockholm), Dr. *Paoletti* (Milano) and Dr. *Peskar* (Bochum). It became apparent that much valid information is available on primary prostaglandins and to some extent on PGI_2, while the metabolism and function of endogenous leukotrienes is much less understood. An interesting observation, reported by Dr. *Kaijser*, was that vasoconstriction in the human forearm after i.v. administration of LTC_4 can be converted into a vasodilation after indomethacin treatment. This suggests that LTC_4 in the peripheral circulation acts partially by stimulating vasodilating eicosanoids release.

Dr. *Vane* also summarized the presently available information on PGI_2, pointing in particular to the significance of its pronounced antiplatelet actions for control of platelet activation in vivo. These antiplatelet actions may be of considerable clinical interest, if platelets are contacted with foreign surfaces, for example during hemoperfusion. Furthermore, other clinical conditions may respond to PGI_2 treatment, such as preeclamptic toxemia, hemolytic uremic syndrome, peptic ulceration, thrombotic complications associated with transplant rejection, prevention of tumor metastases and treatment of pulmonary embolism. The place of treatment with PGI_2 or stable analogues will be defined in the next few years.

Endogenous Variations in Prostacyclin and Thromboxane Biosynthesis

These comments of Dr. *Vane* were collaborated by findings regarding eicosanoid formation and metabolism in pregnancy. According to Dr. *Lippert* (Tübingen), endogenous prostaglandins play an important role in adapting vascular changes in pregnancy, in particular in the uteroplacental region. Increased thromboxane and reduced PGI_2 may be intimately involved in hypertension and thrombosis tendency in preeclampsia, and administration of PGI_2 or related compounds appears to be a promising approach for therapy.

Another disease-related alteration in endogenous eicosanoid production with particular relevance to the clinics is atherosclerosis. Data presented by Dr. *Sinzinger's* group (Wien) suggested that despite the enhanced overall increase in platelet turnover during this process, there may be a different behaviour of "active" and "inactive" atherosclerotic lesions of the vessel wall regarding platelet uptake. Dr. *Fitscha* (Wien) reported an enhanced uptake of platelets into "active" lesions which could be reduced close to that of "inactive" lesions by PGI_2 treatment. Thus, measurement of pathological platelet deposition by suitable methods appears to be a useful tool to monitor the efficacy of PGI_2 treatment in the clinics. Clearly, atherosclerosis is a complex event, and dissociations between different degrees of activity may also help to explain the interesting finding by Dr. *FitzGerald* (Nashville) that patients at advanced stages of atherosclerosis and evidence for platelet activation in vivo have an enhanced endogenous PGI_2 biosynthesis, as assessed by measuring the urinary excretion of PGI_2 metabolites. Although this finding appears to be consistent with a local role for PGI_2 as hemostatic regulator for platelet-vessel wall interactions, further investigations are necessary to define the mechanism(s) behind.

Eicosanoids, Regional Ischemia and Circulatory Shock

Despite serving as precursors for eicosanoid production, polyunsaturated free fatty acids are also subject to lipid peroxidation and may facilitate oxygen centered radical formation. An important issue, dicussed by Dr. *Stam* (Rotterdam), are free radical-associated reactions and their role for cell membrane damage in ischemia. Indeed, generation of reactive oxygen species by polymorphonuclear cells in addition to the release of

enzymatic contents of their granula into the extracellular space may result in a proteolytic attack on viable tissue. The significance of this mechanism for the damage of ischemic myocardium, in particular during early stages of reperfusion, was highlighted by Dr. *Lucchesi* (Ann Arbor). Both neutrophil depletion and administration of radical-scavenging enzymes resulted in improved preservation of the ischemic myocardium in animal experiments and reduced the size of infarct. Thus, a reduced availability of those protective systems will develop during a period of myocardial ischemia, and reperfusion of ischemic myocardium may result in tissue injury which extends beyond that attributed to the ischemic process.

In addition to damaging jeopardized myocardium, fatty acid peroxides may also cause imbalances in PGI_2 and thromboxane formation. As pointed out by Dr. *Parratt* (Glasgow), imbalances can be found between local myocardial release of thromboxane and PGI_2 after coronary artery ligation which may be important for the genesis of arrhythmias, although other factors, in particular catecholamines, should not be ignored.

However, in man the situation may be different. In particular the etiology of myocardial infarction is multifactorial and includes hemorrhages, plaque rupture, vasospasm as well as thrombosis. While most of these events are obviously related to increased local thromboxane production, the initiating step is largely unknown and may be different in different subgroups of patients. As further noted by Dr. *Hirsh* (Richmond), many animal experiments may not be valid for humans because of a different pathophysiology.

Similar conclusions may be drawn for the role of eicosanoids in shock. An early increase in thromboxane generation is probably involved in the early pulmonary hypertension frequently seen in both animal experiments and man. Additionally, there may be a role for leukotrienes regarding changes in permeability. As reviewed by Dr. *Lefer* (Philadelphia), the overall assessment of eicosanoids in shock is a mixed one. While some of them, such as PGI_2 or PGE_1, may act beneficially, others, such as thromboxanes, are rather detrimental. This complex situation makes the intelligent use of eicosanoid-related drugs very difficult.

Clinical Use of Vasodilating Prostaglandins

Numerous studies are available regarding the clinical use of vasodilating prostaglandins, such as PGI_2 or PGE_1, in ischemia associated with peripheral vessel disease. Dr. *Hossmann* (Köln) reviewed data of three