PERSPECTIVES IN PROSTAGLANDIN RESEARCH

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Perspectives in prostaglandin research

With a Special Article by Dr J.R. Vane

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Preface

This book is intended as a review of the First Winter Seminar of the Japan Inflammation Society held on January 28–29, 1983, at the Sasagawa Memorial Hall, Tokyo, Japan. The Japan Inflammation Society was established in 1980, and at the first annual meeting, Dr Bengt Samuelsson was invited as the main guest speaker. For this seminar we invited Dr J.R. Vane from the U.K. and Dr E.J. Goetzl from the U.S.A. One thousand and two hundred people assembled to discuss 'Prostaglandins', including investigators in clinical medicine, pharmacology, biochemistry and other related fields.

Prostaglandins and other arachidonic acid metabolites, which will be collectively referred to as prostaglandins hereinafter, are not only an urgent target of research on inflammation, but have become essential substances in the whole field of medicine. Since volcanos are common in Japan, I would like to compare prostaglandins to an active volcano. This novel group of substances, prostaglandins, seemed to errupt suddenly from the ground of medical science like a new volcano. A large volume of ash is still falling, and covering the entire medical field. Therefore, all medical scientists cannot avoid being strongly affected by this volcano.

Prostaglandins seem to have two faces. One face is evil, bringing about various clinical symptoms of inflammation, and hazardous to every tissue and organ of the body because of inflammation and other problems. The other side is the good face, which alleviates the harmful effects of inflammation, regulates physiological functions of the body, and provides defence against all factors harmful to the body.

In this respect, prostaglandins present a very complicated image, which confuses most people. At present, we need to alleviate this confusion caused by the appearance of prostaglandins. This is the main reason why this meeting was held.

The subjects dealt with in this Winter Seminar were new substances, prostacyclin and leukotrienes, clinical problems concerning atherosclerosis, the kidney, the gastrointestinal tract, and anti-inflammatory drugs. Many other topics have been carried over to the next seminar because of time restrictions.

I believe that this book will be helpful to all investigators and others who would like to review the present status of research and problems concerning prostaglandins in 1983 – because the progress in prostaglandin studies has been so rapid – and this kind of book should be revised at least every year.

Finally, I would like to extend my thanks to the participants to this seminar and in particular to Dr Vane and Dr Goetzl, for their excellent contribution to the meeting. Their presence was essential to the success of this seminar.

Yuichi Shiokawa, M.D.

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This short review is given to beginners in the study of the prostaglandin fields, showing what are prostaglandins.

1. What are prostaglandins ?

The Nobel prize for Physiology and Medicine in 1982 was given to S. Bergström, B. Samuelsson in Sweden and J.R. Vane in U.K. who made great contributions to the study of the prostaglandin fields. Why? Because it has been clarified by them and others that prostaglandins take important and delicate roles in regulation of cell functions in the body.

In shortest words, prostaglandins can be described to be unsaturated fatty acids, which are very potent in pharmacological activities and are formed from the cell membranes, when cells are stimulated, and to modulate delicately the cell functions.

2. How were they discovered?

It was U.S. Von Euler in Sweden in around 1935 that substances in seminal fluid, which contract or relax the uterine muscle, were found to be a kind of unsaturated fatty acids and designated "Prostaglandins (PG)", because he supposed that they may be derived from prostate gland. The major source of prostaglandins in seminal fluid was later found to be vesicular gland, but the name remains to be used. In 1960, S. Bergström determined structures of E and F types of PGs (primary PGs), which were formed from precursor fatty acids. As the content of arachidonic acid (C20:4) in cell membrane is much larger, comparing with other precursor fatty acids (C20:3 or C20:5), the metabolites of arachidonic acid such as PGE_2 or PGF_{2a} are mainly formed in the body. Later it was known that arachidonic acid is converted to PGs through intermediates, PG endoperoxides (PGG_2/H_2)(1973). Thromboxane(TX) A_2 from platelets (1975) and prostacyclin from vascular endothelial cells (1976) were also found and these structures were determined. SRS-A(slow reacting substance of anaphylaxis)

released by antigen from sensitized guinea-pig lung was identified to be a mixture of leukotriene(LT) C_4, LTD_4 and LTE_4. LTs are formed from leukocytes, macrophage, mast cells. Discovery of inhibition of PG biosynthesis by aspirin-like drugs promoted the study of roles of PGs in the body.

3. How are they formed?

PGs, TXs, and LTs are not stored in the cells. Arachidonic acid, a precursor fatty acid, was stored mainly in phospholipids, which are components of the cell membrane. Once the cells are stimulated by binding of agonists to their receptors or even by distortion of the cell membrane, a series of biochemical changes, including calcium influx, occurs and phospholipase A_2 or C is activated. This activation induces the arachidonic acid release, which is the limiting step of the PG formation. Cyclooxygenase converts arachidonic acid to PG endoperoxides, from which PGs and TXA_2 are formed by their own synthetases(Fig.1). Arachidonic acid is also a good substrate of lipoxygenases, which introduce hydroperoxide into one of the positions, e.g. at C-5, 12 and 15 (hydroperoxy-eicosatetraenoic acids, HPETEs). HPETEs become HETEs(hydroxy-eicosatetraenoic acids) or LTs. Acidic nonsterioidal anti-inflammatory drugs such as aspirin inhibit cyclooxygenase at low doses.

Glucocorticoids are introduced into cell nucleus after binding with a receptor protein in cytoplasm, stimulate the synthesis of RNA, and then that of a protein, which is called as lipomodulin or macrocortin. This protein inhibits phospholipase A_2 or the arachidonic acid release.

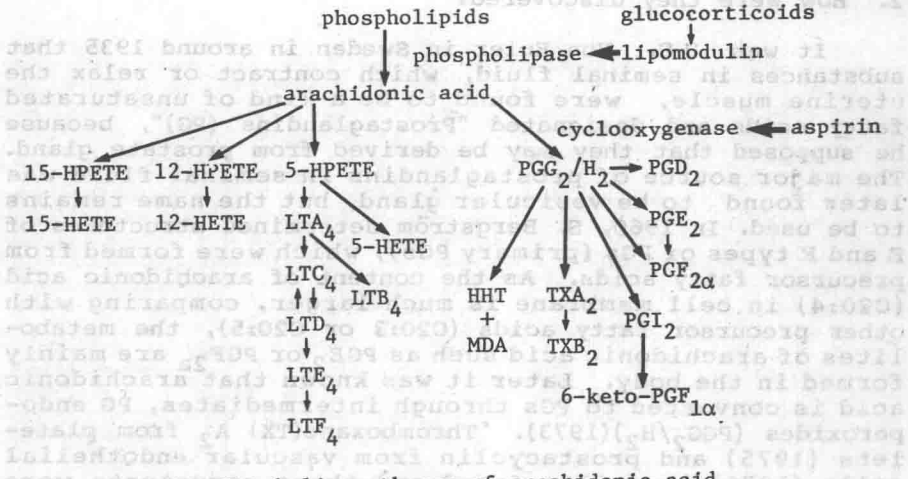

Fig. 1. Metabolic pathways of arachidonic acid.
←: inhibition

This indicates that glucocorticoids inhibit the formation of products of lipoxygenase as well as cyclooxygenase.

As most of the cells in the body store arachidonic acid, and contain synthetases, they could synthesize the metabolites, which modulate the cell functions. A single type of cells may not be considered to form all of the metabolites, but final major active product(s) may be selected for cell types, for example, TXA_2 for platelets, PGI_2 for vascular endothelial cells. Lipoxygenases are also contained in certain cells, such as leukocytes, mast cells, platelets.

Arachidonic acid metabolites are also easily destroyed. The half-lives of TXA_2, PGI_2 and PGG_2/H_2 in aqueous solution at 37° C, at neutral PH are only 30 sec, 2 min and 5 min, respectively and they are destroyed non-enzymatically to TXB_2, 6-keto-PGF_{1a} and other PGs, respectively. PGE_2 and PGF_{2a}, although rather stable in aqueous solution, are inactivated by 15 hydroxy-PG dehydrogenase by over 90% in a single passage of the pulmonary circulation. Thus, the body regulates their cellular functions beautifully using these easily synthesized and inactivated prostanoids.

4. What are their pharmacological actions?

The pharmacological actions of the metabolites are different from one to another and sometimes reverse. This wide difference in the actions is essential for the eicosanoids, e.g. PGF_{2a} is different from PGE_2 in structure, only carrying hydrogen at C-9 position, but contracts bronchial smooth muscle, instead of relaxation by PGE_2. Thus, it is quite difficult to describe their pharmacological actions, as a whole. Table 1 lists the major actions of the prostanoids. It may be the wisdom of God that the body synthesizes from a single material, arachidonic acid, a variety of the products, which are slightly different in the structure, but markedly

Table 1. Pharmacological actions of arachidonic acid metablites.

a.	Smooth muscle contracion or relaxation (ileum, stomach, bronchus, uterus etc.)(most of PGs,TX, LTs)
b.	Arteriolar dilatation (PGE_2,PGI_2)(PGE_1)
	contraction(LTC_4,LTD_4,TXA_2,PGF_{2a}(?))
c.	Plasma exudation (LTC_4,LTD_4)(PGE_2,PGI_2 potentiation)
d.	Platelet aggregation (TXA_2,PGG_2/PGH_2)
	inhibition (PGI_2,PGD_2,PGE_1)
e.	Chemotaxis and chemokinesis (LTB_4,HETEs,HHT)
f.	Inhibition of gastric acid secretion (PGE_2,PGI_2)
g.	Peripheral nerves---sensitization of pain receptors, inhibition of norepinephrine release
f.	Others

different in pharmacological actions.

5. What roles do they play?

It is difficult to describe the whole examples in a short review, since the prostanoids are in a variety of the pharmacological actions and most of the cells carry the ability to form the prostanoids, which regulate effectively the cell functions. Here, three examples are described.

If prostanoids may take a common role in the body, they might act as "modulators", which are not the principal actors in cellular functions and support the actions of the leading actor or actress from the side, shown as a role of PGE in negative feedback loop in norepinephrine release from adrenergic nerve endings.

a. Reproductive physiology

Typical physiological roles of the arachidonic acid metabolites are taken in reproduction. PGE_2 and PGF_{2a} formed in the ovarian follicle take an important role in expulsion of an ovum from matured follicle. After the follicle is transformed to corpus luteum, an order to cease the progesterone secretion comes from uterus using PGF_{2a}. Thus, PGF_{2a} is involved to sex cycle. Uterine contraction in labour is induced by PGF_{2a} or PGE_2, formed from myometrium or amnion. Use of PGF_{2a} and PGE_2 for induction of labour is based on this fact.

b. Inflammation

The pharmacological action of the arachidonic acid metabolites may lead us easily to suppose involvement of these metabolites in acute inflammatory reactions. In fact, endogenous PGE_2 and PGI_2 induce arteriolar dilatation, which causes local redness and heat in initial response of the inflammation. By the increased local blood flow, PGE_2 and PGI_2 potentiates the plasma exudation induced by histamine or bradykinin and this causes local edema. LTC_4 and LTD_4 by themselves exude plasma protein from venules. Leukocyte migration is accelerated by LTB_4, HETEs and HHT.

Bradykinin induces pain through PGE biosynthesis near the pain receptors, which is sensitized by PGE produced. E type of prostaglandin is also involved in fever. These findings provide clear explanation of anti-pyretic, analgesic and anti-inflammatory actions of aspirin-like drugs by the inhibition of cyclooxygenase.

In allergic inflammation or anaphylaxis, LTs and HETEs are detected in inflammatory exudates. LTC_4 and LTD_4, potent bronchoconstrictive prostanoids, may be involved in bronchial asthma.

c. Thrombosis

The thrombus formation in artery causes cardiac

infarction, cerebral thrombosis, DIC and occasionally leads to death. The inhibition of the platelet aggregation, a trigger of the thrombus formation, is essential to control and therapy of the thrombosis.

Prostacyclin (PGI_2) from endothelial cells may protect the platelet adhesion to the endothelial cell wall. Once the endothelial cells are desquamated, the circulating platelets aggregate on the subendothelial layer in releasing the contents of the granules and cover the defects.

ADP, 5-HT and TXA_2 released from the platelets lead other platelets to aggregate at the injured subendothelial layers. The release reaction requires TXA_2, which is formed in the membrane from arachidonic acid by stimuli to the platelets. Aspirin-like drugs inhibit cyclooxygenase, and hence the release reaction and aggregation by inhibition of the TXA_2 formation. Large doses of aspirin did not necessarily prevent cardiac infarction, probably because of simultaneous inhibition of prostacyclin(PGI_2). The PGI_2 formation from the endothelial cells is reported to be declined in aging and in certain diseases, in which replacement therapy by exogenous PGE_2 might be necessary.

d. Others

PGE_2 and PGI_2 are produced in kidney and gastric mucosa and may play an important role in blood flow regulation in both organs and inhibition of acid secretion in stomach, but the precise role remains to be elucidated.

The bone metastasis of solid tumors causes bone absorption. PGE_2 released from tumors or connective tissues may induce the appearance of osteoclasts to release calcium from bone.

7. How are they applied in clinical fields ?

The clinical applications can be divided by two parts; use of prostaglandins and their analogues as drugs and regulation of arachidonic acid metabolism by drugs.

a. PGs as drugs.

The induction of labour is one of targets for PGF_{2a}, PGE_2 and their analogues. Vaginal use of tablets for this purpose, besides intravenous administration, has been developed.

PGE_1 and PGI_2 are used to expect the inhibition of platelet aggregation and vasodilatation. PGI_2 is unstable and requires pharmaceutical device. So PGE_1 is replaced to PGI_2, but fifty to a hundred times more dose of PGE_1 is necessary for intravenous infusion than for intraarterial infusion. Recently stable and orally effective analogues of PGI_2 has been developed.

b. Drugs as regulators of arachidonate metabolism

i) Cyclooxygenase inhibitors

Acidic non-steroidal anti-inflammatory drugs such as

aspirin are used to expect analgesic, anti-pyretic and anti-inflammatory actions. Anti-thrombotic action is added to the actions of these drugs.

ii) Thromboxane synthetase inhibitors

While aspirin-like drugs inhibit the formations of both TXA_2 and PGI_2 through the inhibition of cyclooxygenase, thromboxane synthetase inhibitors, which inhibit selectively the TXA_2 formation, are superior anti-thrombotic agents to aspirin by allowing prostacyclin formation by vascular endothelia. Imidazole and pyridine compounds have been developed and are reported to be effective against cardiac infarction and angina. In in vitro experiments, these compounds inhibit the platelet aggregation induced only by threshold doses of aggregating agents.

iii) PGI_2 potentiators in platelet aggregation and PGI_2 biosynthesis accelerators.

PGI_2 inhibits platelet aggregation by accumulation of cyclic AMP through activating adenylate cyclase. Thus, agents, which show inhibitory activity of phosphodiesterase, inhibit platelet aggregation in large doses by themselves and potentiate the anti-aggregating activity of PGI_2 in smaller doses. Dipyridamole and phthalazinol (7-ethoxycarbonyl-6,8-dimethyl-4-hydroxymethyl-1(2H)-phthalazinone) are the example.

Several vasodilators are claimed to induce the PGI_2 formation. Phenol compounds such as MK-447 also accelerate PGI_2 formation from rat aortae.

iv) Lipoxygenase inhibitors

Lipoxygenase products, like leukotrienes, may be involved in allergic inflammation or bronchial asthma, although the precise roles have not yet known. Selective inhibitors of 5-lipoxygenase may elucidate the real roles of the products.

v) Eicosapentaenoic acid (EPA)

The findings that Eskimos, who show high ratio of EPA/AA (arachidonic acid) in blood, are rarely affected by cardiac infarction, prompted us to consider that uptake of EPA might induce inhibition of platelet aggregation and prevention of thrombosis. It is not yet known whether EPA uptake in long term may prevent cardiac infarction.

The short review was mainly intended for beginners to get the outline of arachidonic acid metabolism and their roles in the body. It is my greatest pleasure if readers could be helped to understand easily the following special lectures, and papers in symposia and posters. Readers, who would like to study further this field, are recommended to read e.g. the series of Advances in Prostaglandins, Thromboxanes and Leukotrienes Research (Vol.1-12), Raven Press.

Special lectures