Advances in Prostaglandin Research

Practical Applications of Prostaglandins and their Synthesis Inhibitors

Edited by

S. M. M. Karim

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Preface

This is the fourth in a series of books on *Advances in Prostaglandin Research* published by MTP Press. From laboratory and animal studies a large number of practical applications of prostaglandins have been identified. In some areas clinical trials have also been carried out. There is usually a long time interval between identifying practical applications of new drugs and clinical trials. Most of the information on practical applications of prostaglandins is scattered in different journals.

Although a number of books dealing with prostaglandin research have been published (including some on practical applications in specific areas, e.g. reproduction) there is no single volume dealing with all areas of practical applications of these substances. This book aims at filling this gap and should be of interest to clinicians as well as to medical and basic scientists in academic institutions and in the pharmaceutical industry.

In some areas, exciting potential applications of prostaglandins have been identified from basic research but clinical trials have so far not been carried out. Such areas of practical applications are covered in a separate introductory chapter.

All contributors to the volume are scientists and clinicians actively engaged in prostaglandin research and most are recognized authorities in specific areas. The need for rapid publication in a fast-expanding field is obvious. Attempts have been made to cover work published until the end of 1978 (admittedly, some omissions are inevitable) and publication date set for June 1979. This has only been possible as a result of the co-operation of the contributors in submitting their manuscripts on time and the efforts of the publishers in bringing the book out within 3 months of receiving the manuscripts. Because of the tight schedule involved, all proof checking was carried out by the Editor and his staff. I would like to apologize to the contributors and to readers for any inadvertent errors.

Tables and figures previously published are, in general, acknowledged by a reference in the legends and I am grateful to the respective authors, editors, and publishers for their permission.

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Singapore
February, 1979

Sultan M. M. Karim

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General Introduction and Practical Implications of some Pharmacological Actions of Prostaglandins, Thromboxanes and their Synthesis Inhibitors

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1.1 INTRODUCTION

In almost every branch of medicine there is an intense interest in the prostaglandins (PG), thromboxanes (TX) and inhibitors of their actions or biosynthesis. The study of these substances has already significantly advanced our understanding of several biological processes.

The hope that prostaglandins will further provide the missing link in hitherto unknown biological mechanisms is overwhelming amongst scientists working in the field as is the prospect of valuable therapeutic agents or diagnostic tools resulting from their investigation.

Several practical applications of prostaglandins and their synthesis inhibitors have already been identified. In some of these areas clinical trials have also been conducted. These are reviewed in individual chapters that follow. The purpose of this section is to provide an introduction to the biosynthesis of prostaglandins and thromboxanes and to review potential practical applications of prostaglandins not covered in individual chapters.

1.2 BIOSYNTHESIS OF PROSTAGLANDINS AND THROMBOXANES

A selective introduction to the synthesis of prostaglandins and thromboxanes and the actions of their inhibitors is necessary to an understanding of their therapeutic usefulness and drawbacks (Figure 1.1). A more detailed treatment has been published elsewhere (Hillier, 1978; Vane, 1978).

No tissue stores prostaglandins or thromboxanes as far as we know; they are synthesized upon acceptance of a suitable physiological, pharmacological or pathological signal. The enzymes only act upon free polyunsaturated fatty

acids such as arachidonic acid to form prostaglandins and thromboxanes. Therefore, a prior requirement is the former's release from phospholipids, triglycerides and cholesteryl esters, where it is in a bound form and unusable as a substrate for prostaglandin-forming enzymes. In some tissues the availability of free fatty acid is the rate-limiting step in synthesis and an appropriate trigger mechanism would be the activation of phospholipase to

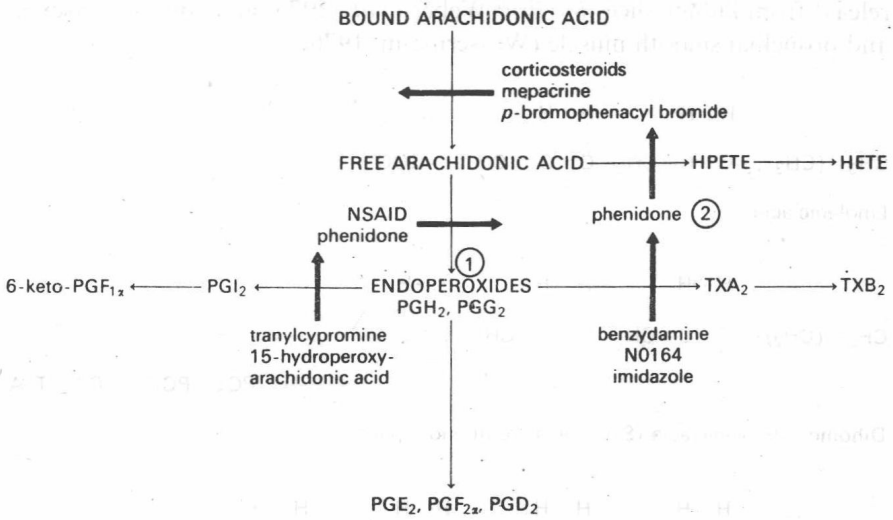

Figure 1.1 Inhibitors of the metabolism of arachidonic acid via the cyclo-oxygenase (1) and lipoxygenase (2) pathways.

1-phenyl-3-pyrazolidone, phenidone (Blackwell and Flower, 1978) inhibits arachidonic acid metabolism by both pathways. References for other inhibitors; corticosteroids (Nijkamp *et al.*, 1976), mepacrine (Vargaftig and Dao Hai, 1972), *p*-bromophenacyl bromide (Mitchell *et al.*, 1977), NSAID (Flower, 1974), tranylcypromine (Gryglewski *et al.*, 1976; Myatt and Elder, 1977), imidazole (Nijkamp *et al.*, 1977), benzydamine (Moncada *et al.*, 1976), N0164 (Eakins and Kulkarni, 1977), 15-hydroperoxy-arachidonic acid (Moncada *et al.*, 1976). Substrate analogues will also inhibit pathway (1) (Lands and Rome, 1976)

NSAID: non-steroidal anti-inflammatory drugs
HPETE: 12-hydroperoxy-arachidonic acid
HETE: 12-hydroxy-arachidonic acid

liberate the free fatty acid from a phospholipid when it can be acted upon by appropriate synthetase enzymes. Availability of appropriate enzymes may also limit prostaglandin formation but this is generally considered to be less important.

The type of precursor fatty acid present determines the prostaglandin formed. The majority of investigators have studied arachidonic acid which is converted to PGE_2, $PGF_{2\alpha}$, PGG_2, PGH_2, TXA_2, TXB_2 and PGI_2. However, it should be noted that arachidonic acid is obtained by desaturation of dihomo-γ-linolenic acid (Figure 1.2). This relative of arachidonic acid can

be converted to form different prostaglandin and thromboxane end-products which may have very altered properties from those formed from arachidonic acid. The types of tissue prostaglandins and thromboxanes formed may be modified by dietary intake of different types of polyunsaturated fatty acids.

The next vital step in prostaglandin synthesis is the formation of the common intermediate endoperoxides. PGG_2 and PGH_2. These are unstable but do possess biological activity. They can, for example, stimulate renin release from kidney slices *in vitro* (Weber *et al.*, 1976) and contract vascular and bronchial smooth muscle (Wassermann, 1976).

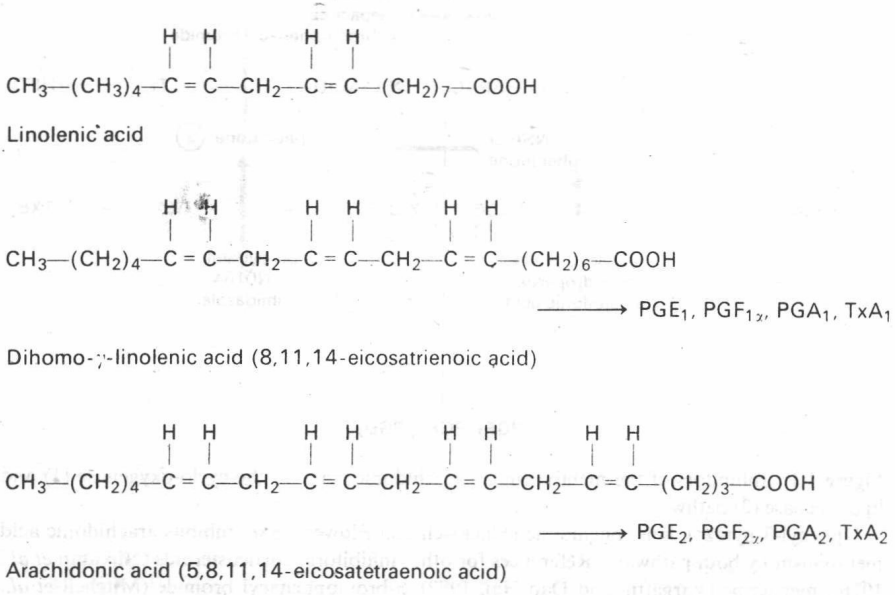

Figure 1.2 Prostaglandins and thromboxanes formed from unsaturated precursor fatty acids

A wide variety of tissues possess the ability to synthesize prostaglandins from arachidonic acid (Christ and van Dorp, 1972). Their capacity to do so *in vitro*, however, is very variable. For example, *in vitro* seminal vesicle prostaglandin-synthesizing enzymes can convert 75% of substrate to prostaglandins whereas brain tissue converts 1% or less. How this relates to *in vivo* production is unclear but even 1% conversion may represent a level sufficient for the needs of the tissue. A distinct problem when studying *in vitro* synthesis (or *in vivo* synthesis after surgical manipulation) is a transient stimulation of prostaglandin production by trauma unrelated to the normal physiological control mechanisms. Thus unless adequate time is allowed between handling and carrying out measurements, erroneous concentrations may be measured. Notwithstanding these reservations, it is clear that different tissues have varied capacities (qualitatively and quantitatively) to form prostaglandins. Thus platelets can largely (but not exclusively) form TXA_2

when induced to aggregate since they predominantly contain the thromboxane synthesizing enzymes and co-factors to form this compound. On the other hand blood vessels and uteri form predominantly PGI_2, and kidneys PGE_2 and $PGF_{2\alpha}$. The importance of these differences is discussed later but clearly they demonstrate the ways in which selectivity can be present between tissues and indeed between cells. *In vitro* studies of prostaglandin synthesis may be misleading unless careful account is taken of the laboratory conditions used including the addition of co-factors. For example, sheep uterine microsomes and seminal vesicle microsomes form large amounts of PGE_2 and $PGF_{2\alpha}$ in the presence of reduced glutathione but at low substrate concentrations (and without co-factors or with only haemaglobin and tryptophan added) they form largely 6-keto-$PGF_{1\alpha}$ (Dighe *et al.*, 1978; Cottee *et al.*, 1977).

The type of prostaglandin or thromboxane formed in the body can be manipulated by dietary adjustment or by blocking the enzymeq that form a particular prostaglandin. For example, it has been found that an enzyme exists (PGE_2-9-keto reductase) in some tissues that converts PGE_2 to $PGF_{2\alpha}$. The difference in properties of these prostaglandins makes the occurrence of this enzyme of importance. In rats it has been shown that a high salt diet increases the activity of this enzyme 2–3 fold and this can alter renin release and sodium absorption (Weber *et al.*, 1977). The overall prostaglandin formation in the body in man can be increased by feeding a subject arachidonic acid. This increases arachidonate in platelets and significantly increases the aggregation of platelets by adenosine diphosphate (ADP). At the same time the major urinary metabolite of PGE (7α-hydroxy-5,11-di-keto-tetranorprostane-1,16-dioic acid) is also increased. Seyberth *et al.* (1975) administered ethyl arachidonate to man for 2–3 weeks and increased the arachidonate in phospholipids, triglycerides and cholesterol esters. Free arachidonate in plasma was not altered. Dietary factors influencing the prostaglandin forming capacity in lungs have also been established. Meydani, Mathias and Schatte (1978) showed that $PGF_{2\alpha}$, PGE_2 and PGE_1 formation in lungs of rats fed a high (78%) polyunsaturated fatty acid diet (PUFA) was significantly higher than in rats fed a low (5%) PUFA diet. However, no data on thromboxane or PGI_2 formation are available.

Normally in platelets, arachidonic acid is predominant and, with appropriate stimuli, the pro-aggregatory TXA_2 and endoperoxides PGG_2 and PGH_2 are formed and accompany aggregation (Hamberg *et al.*, 1975). The prostaglandins and thromboxanes formed in platelets can be redirected to those of the '1' series by feeding dihomo-γ-linolenic acid, the precursor of prostaglandins and thromboxanes with one unsaturated double bond. Thus, endoperoxides PGG_1 and PGH_1, PGE_1 and possibly TXA_1 are formed with the greater availability of dihomo-γ-linolenic acid and these have less pro-aggregatory action than products formed from arachidonic acid (Falardeau *et al.*, 1976). Kernoff *et al.* (1977) detected reduced plasma heparin-neutralizing

activity and reduced platelet aggregation in volunteers fed dihomo-γ-linolenic acid and suggest that this manipulation has potential in treating human thromboembolic disease. However, the discovery by Vane's group (Moncada *et al.*, 1976a) that blood vessel endothelium forms predominantly prostacyclin (PGI_2) from arachidonic acid has necessitated a rethink of the desirability of using dihomo-γ-linolenic acid for treating thromboembolic disease. PGI_2 potently inhibits the adherence of platelets to blood vessel walls. Thus, the increased presence of substrate other than arachidonic acid may inhibit the vascular formation of PGI_2 and, therefore, interfere with the anti-adherent properties of the endothelium. Dihomo-γ-linolenic acid therapy therefore probably does not represent the ideal treatment for thromboembolic disease although further study is clearly warranted.

In the same area, aspirin and sulfinpyrazone have been studied for their ability to prevent myocardial reinfarction. Although pathological studies of the relation between coronary thrombosis and myocardial infarction have yielded conflicting results, much evidence points to occlusive thrombosis being an important factor in myocardial infarction (Chandler *et al.*, 1974). Aspirin in high doses inhibits the cyclo-oxygenase enzymes and, therefore, reduces TXA_2 and PGI_2 formation; the former effect is beneficial in preventing arterial thrombosis but the latter is not. However, although the effect of aspirin on platelet cyclo-oxygenase persists for the duration of the life span of the platelet, the inhibition of vascular enzymes is more transient because of the new protein synthesizing ability of vessels. It is, therefore, likely that modest doses of aspirin will desirably have a greater effect on pro-aggregatory TXA_2 synthesis than on PGI_2 (Vargaftig and Lefort, 1977). Sulfinpyrazone also inhibits prostaglandin formation (Anturane Reinfarction Trial, 1978) and therapy with this drug has had some success in reducing myocardial reinfarction. The ideal therapy in terms of a prostaglandin approach is probably via selective inhibition of TXA_2 synthesis (Moncada and Vane, 1978).

The actions of selective inhibitors of TXA_2 synthesis (such as imidazole and azo analogues of the prostaglandins) make more endoperoxides available for conversion to other prostaglandins (Figure 1.1). Thus, in platelet suspensions in the presence of these selective inhibitors, less thromboxane is formed. Simultaneously, a greater amount of PGE_2 is synthesized (Fitzpatrick and Gorman, 1978). Thus, the effects of induced reduction of a particular prostaglandin may be masked by the presence of greater amounts of others.

Progressive research has identified a number of selective inhibitors of prostaglandin and thromboxane synthesis (see Figure 1.1 for references). These are only relatively specific at moderate dose levels; higher doses reduce selectivity. Phenidone (1-phenyl-3-pyrazolidone) blocks both the lipoxygenase and cyclo-oxygenase pathways in horse platelets and guinea-pig perfused lungs (Blackwell and Flower, 1978) and should be a useful tool for the investigation of the lipoxygenase pathway.

Recent studies involving thromboxanes and platelet aggregation and the effects of commonly used therapeutic agents on this system have helped to explain their unwanted and previously unexplained side-effects. For example, oral contraceptives increase the platelet microsomal content of pro-aggregatory prostaglandins and thromboxane forming enzymes (Schorer *et al.*, 1978). Similar changes occur in smokers (Gerrard *et al.*, 1976) and diabetics (Halushka *et al.*, 1977). Likewise the antithrombotic effects of some therapeutic agents can be explained in terms of prostaglandin drug interaction.

In a recent paper Horrobin *et al.* (1978c) suggest that TXA_2 is a negative feedback regulator of other products formed from arachidonic acid. They confirmed that inhibition of TXA_2 synthesis with imidazole or furosemide or antagonism of TXA_2 action with diazepam leads to greater PGE_2 and $PGF_{2\alpha}$ synthesis. In guinea-pig lung and platelets, the increased prostaglandin synthesis is greater than could be accounted for simply by diversion of endoperoxide to the prostaglandin pathway. Horrobin *et al.* (1978a) evoke the inhibition of TXA_2 as the mechanism of action of dipyridamole in inhibiting platelet aggregation. They suggest that TXA_2 promotes while PGI_2 inhibits calcium release from platelet stores. Dipyridamole inhibits TXA_2 synthesis and prevents calcium mobilization and ensuing aggregation. However, the indirect evidence they present is countered by data of Moncada *et al.* (1978) who showed that dipyridamole does not prevent the conversion of PGH_2 to TXA_2 in rabbit, horse and human platelet preparations. This group suggested that the antithrombotic effect of dipyridamole (a phosphodiesterase inhibitor) is due to stimulation of cAMP in platelets by PGI_2 (Moncada and Korbut, 1978). PGI_2 released from the pulmonary circulation activates cAMP and this effect is enhanced by dipyridamole. Consistent with this is the greater effect of dipyridamole in arterial than in venous circulation and the antagonism of its action by PGI_2 antiserum and by high doses of aspirin which reduce circulating concentrations of PGI_2. However, Jorgensen and Stoffersen (1978) showed that dipyridamole has an inhibitory effect on platelets which is independent of PGI_2 or TXA_2 but dependent upon albumin concentrations. If prostaglandin and thromboxane synthesis is inhibited by aspirin, dipyridamole in fact enhances thrombin-induced aggregation but increasing albumin concentrations reverse this effect allowing an inhibition of aggregation.

1.3 CENTRAL NERVOUS SYSTEM

The practical implications of the prostaglandins and thromboxanes in CNS function deserve only modest mention at this time although future investigations will certainly alter this as the area is one of continuing research and development. The most widely studied aspect of prostaglandins and brain function is in fever, although they have also been implicated in the mechanisms of action of antidepressant drugs, in analgesia, schizophrenia,

cerebral circulation, neuronal transmission and behaviour (see Hillier, 1977 for references).

In recent studies on the role of prostaglandins in controlling body temperature (see Hillier, 1977 for references) it has been shown that intraventricular arachidonic acid causes shivering and dose-related hyperthermia. Additionally, PGE_2 is raised in CSF during certain types of pyrogen fever and can increase temperature in humans in pharmacological doses. Administration of non-steroidal anti-inflammatory drugs to pyrexic animals results in lowered temperature and a parallel decrease in PGE_2 in the CSF. However, evidence that prostaglandins are mandatory mediators of fever is equivocal. Pyrogens can evoke fever in animals that do not respond to prostaglandin administration with hyperthermia (Veale and Cooper, 1975) and elevated levels of prostaglandins are not always seen in pyrogen-induced fever (Cranston *et al.*, 1975). More recently two sub-groups of fever developing after pyrogen administration have been described. The first, seen in animals not previously exposed to pyrogens, had a long latency before hyperthermia, whereas a second sub-group that had on a previous occasion been exposed to pyrogens had a short latency period before hyperthermia on subsequent pyrogen administration. In the latter type, PGE and PGF increased in parallel with the rising body temperature but in the former no significant increase in prostaglandins was noted (Milton *et al.*, 1977). It therefore remains to be decided whether prostaglandins are pathological mediators of pyrogen-induced fever.

Investigations are being carried out in an attempt to link prostaglandins with mental illness. At this time there is little concrete scientific evidence but further investigation is clearly warranted. Horrobin (1977, 1978) has suggested that schizophrenia is a 'prostaglandin-lack disease'. It is hypothesized that schizophrenia is related to excessive functional dopaminergic activity and almost all anti-schizophrenic drugs block dopamine receptors which are involved in stimulating prolactin production and release. Horrobin *et al.* (1978b) have shown that this stimulates prostaglandins. Schizophrenics are said to be resistant to pain and arthritis and prostaglandins have been implicated in these pathological states. Schizophrenia can be transiently relieved by fever (when PGE increases) and platelets from schizophrenics do not produce PGE_1 normally when stimulated by ADP (Abdulla and Hamadah, 1975). High doses of prostaglandin inhibitors cause schizophrenia-like symptoms. More recently, it has been shown that PGE_1 induces a smaller increase in [^{3}H]cyclic AMP in platelet rich plasma from schizophrenics compared with normal individuals (Rotrosen *et al.*, 1978). This suggests that reduced sensitivity as well as inhibition of prostaglandin synthesis is evident in schizophrenics but there is little to explain whether this prostaglandin lack is a cause or an effect of the disease.

However, some anti-schizophrenics such as clozapine do not increase prolactin release and, by inference, prostaglandin synthesis. Tricyclic anti-