TOPICS IN THERAPEUTICS 5

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FOURTH EDITION

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EDITORS' PREFACE

The continuing popularity of the Topics in Therapeutics conferences at the Royal College of Physicians is ample testimony to the interest of doctors in the scientific approach to the benefits and hazards of modern medical treatment, and justifies the continuing publication of the proceedings. We hope that this volume will appeal both to those who were present at the Conference, and to those who were unable to attend.

We would like to express our thanks to the chairmen of the several sessions; the contributors; and Miss Gillian Andrew, Conference Secretary of the Royal College of Physicians, and her colleagues for their help in making the conference such a success. We are also grateful to Mrs Betty Dickens and the staff at Pitman Medical Publishing Company, and to our Secretary, Mrs Vivienne Leach, for their help in producing this book.

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PROSTAGLANDIN PHARMACOLOGY

E W Horton

The pharmacological actions of prostaglandins are of interest, because of their therapeutic implications. However, the bewildering diversity of their actions on different cell types, tissues and organs may mitigate against such therapeutic application. Moreover, the natural prostaglandins may be metabolised rapidly, fail to be absorbed after oral administration, or be incapable of penetrating certain barriers in adequate concentrations. These and other pharmacokinetic problems are familiar to the pharmacologist, particularly the clinical pharmacologist.

To overcome such deficiencies, an approach widely used by the pharmaceutical manufacturers is to synthesise new chemicals similar to the natural compound, but differing from it structurally. Many such synthetic analogues of the natural prostaglandins have been prepared in recent years. Some have greater selectivity of pharmacological actions, some are less readily inactivated, whilst others when taken by mouth are more effective than the naturally-occurring compounds.

Origin of the Natural Prostaglandins

Prostaglandins were originally detected in human seminal plasma, using biological tests, and human semen is still the richest known mammalian source of these substances. Prostaglandins occur naturally in the tissues of almost all animal species so far studied. Their distribution ranges from Man down to the lowly coral, *Plexaura homomalla.* Some plants also contain prostaglandins, and several micro-organisms possess enzyme systems for prostaglandin metabolism.

Natural prostaglandins are not stored in cells but are synthesised very rapidly from unsaturated, long-chain fatty acids, in response to an appropriate stimulus. The amount of prostaglandin released from an organ in response to a stimulus far exceeds the total prostaglandin content of the organ prior to stimulation. Release

of prostaglandins from an organ can therefore be equated with new synthesis. The stimuli capable of initiating prostaglandin synthesis and release are numerous and diverse. They may be physical (mild stretch, intraluminal foreign bodies, emboli, trauma, and phagocytosis of colloidal particles) or chemical (classical hormones of the peptide, amine, or steroid groups; local hormones such as histamine and 5-hydroxytryptamine; concentration changes in oxygen and ions, notably sodium; and drugs, for example, tubocurarine). Finally, stimulation of many adrenergic nerves and some cholinergic nerves increases prostaglandin concentration in the venous effluent from the stimulated organ.

Biosynthesis and Metabolism of Prostaglandins

Natural prostaglandins are derived mostly from arachidonic acid, less commonly from its precursor dihomo-γ-linolenic acid and more rarely from the corresponding 20 carbon acid with five double bonds. In this paper discussion will be restricted, for the most part, to derivatives of arachidonic acid (Figure 1). It must be stressed, however, that biosynthesis of prostaglandins can account for only a minute fraction of total arachidonic acid turnover. Non-prostaglandin derivatives of arachidonic acid, although of possible biological importance, will not be mentioned further here.

It seems unlikely that cellular concentrations of free arachidonic acid are sufficiently high to account for the amounts of prostaglandins which can be so rapidly synthesised. The present evidence suggests that the precursor arachidonic acid is chemically bound as an ester in the '2' position of the membrane phospholipid molecules. The first step in prostaglandin synthesis must therefore be the liberation of free arachidonic acid by hydrolysis catalysed by phospholipase A_2. Evidence is fast accumulating in favour of this hypothesis; moreover, there is substantial evidence in support of the view that steroids such as hydrocortisone, prednisolone, and dexamethasone owe their anti-inflammatory actions to the inhibition of this arachidonic acid mobilisation from phospholipids, thus reducing the concentration of precursor acid and so indirectly reducing prostaglandin synthesis. There is as yet no clear evidence that these steroids inhibit the phospholipases themselves.

Other sources of arachidonic acid must, however, be kept in mind, notably the cholesterol esters so abundant in the adrenals and ovaries, and the neutral lipids found in adipose tissue and plasma.

The first step/s in prostaglandin synthesis proper is catalysed by the microsomal enzyme, fatty acid cyclo-oxygenase. This converts arachidonic acid to the endo-peroxide, PGG_2 and thence to its reduced form, PGH_2 (see Figure 1). It is from the latter compound that most of the natural prostaglandins are thought to be derived. The now classical prostaglandins, PGE_2 and $PGF_{2\alpha}$ are formed from PGH_2 by the action of an isomerase and reductase respectively.

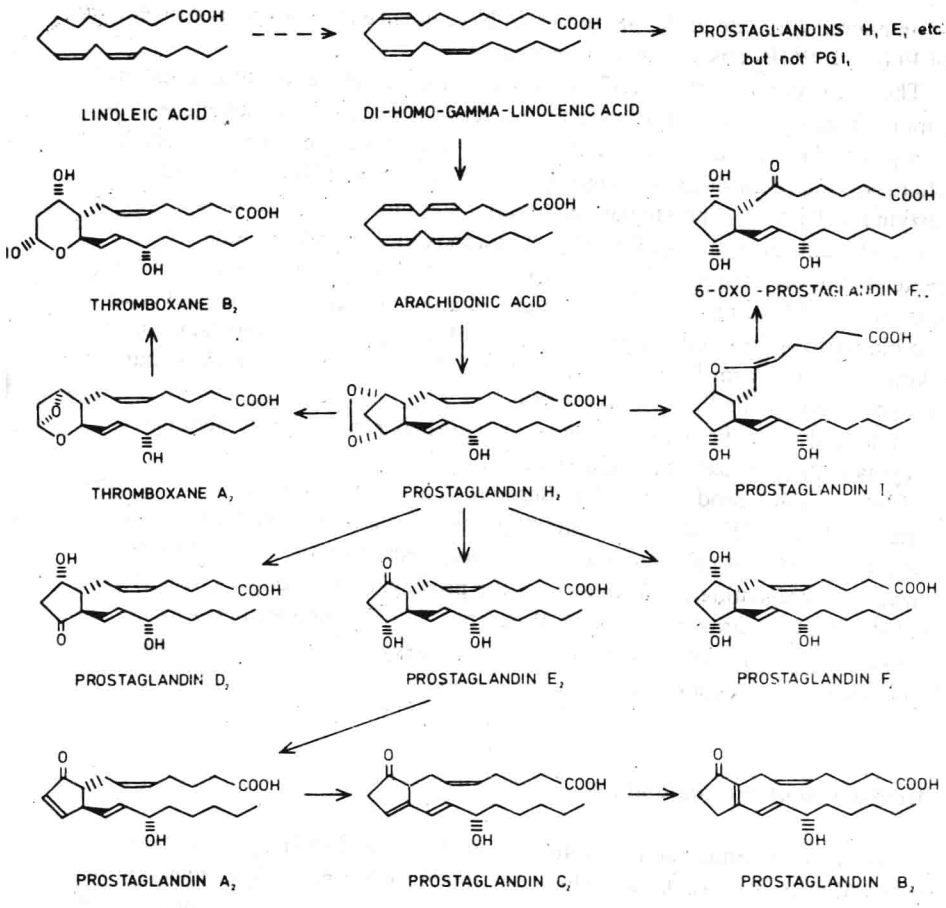

Figure 1 Biosynthesis of prostaglandins

The less well known PGD_2, also formed from PGH_2, is catalysed by a different isomerase (PGD isomerase).

There is still controversy over the existence of an enzyme which will dehydrate PGE_2 to PGA_2, though much evidence suggests that PGA_2 may have a pathophysiological role in sodium balance and control of blood pressure. The conversion can be achieved non-enzymatically with ease by the treatment of PGE_2 with acid. For this reason, many of the claims to have identified PGA_2 as a natural compound may be based upon the formation of an artefact during extraction. There is certainly an isomerase in animals for the conversion of PGA_2 to PGC_2, though this enzyme has not yet been found in man. Finally, the isomerisation of PGC_2 to PGB_2 proceeds rapidly under alkaline conditions and

at an appreciable rate at the pH of blood. No evidence for enzymatic conversion of PGC_2 to PGB_2 has yet been produced.

The most recently discovered prostaglandins are both highly labile substances rapidly inactivated by hydration in the presence of water. Thomboxane A_2 has a non-prostaglandin name because it lacks the 5-membered carbon ring which is characteristic of all other prostaglandins. Nevertheless, TXA_2 is formed enzymatically from a prostaglandin (PGH_2) and must be regarded as one of the prostaglandin (or prostanoid) family. Thromboxane synthetase, abundant in platelets but also found in lung and spleen, is the enzyme responsible for this conversion. TXA_2 has a half-life in water of about 30 seconds, it is converted to the biologically less active thromboxane B_2. Prostaglandin I_2 (prostacyclin) is likewise formed from PGH_2 by the enzyme, PGI_2 synthetase, which is found in the endothelial cells lining blood vessels.

In neutral or acidic aqueous conditions, PGI_2 is rapidly inactivated non-enzymatically to 6-oxo-prostaglandin $F_{1\alpha}$.

The enzymatic production of all these prostaglandins and of those of the other series (PGE_1, PGE_3, etc) is inhibited by non-steroidal anti-inflammatory drugs such as aspirin and indomethacin. These drugs act upon the cyclo-oxygenase enzyme so preventing the formation of the prostaglandin endoperoxides (PGD_2 and PGH_2) from arachidonic acid. When the cyclo-oxygenase pathway is blocked in this way, increased amounts of hydroxylated (non-prostaglandin) derivatives or arachidonic acid may be formed.

Metabolism of Prostaglandins

Following intravenous administration, both PGE_2 and $PGF_{2\alpha}$ are rapidly removed from the circulation. Thus, one minute after intravenous injection of labelled PGE_2 into one arm, blood collected from a vein in the volunteer's other arm was found to contain an amount equivalent to the presence of no more than 4% of the original unmetabolised PGE_2 in the whole circulation, though 40% was present in the circulation in the form of a lung metabolite, 15-oxo-13, 14-dihydro-PGE_2. Perfusion experiments with lungs *in vivo*, autoradiographic studies, and other radio-isotope measurements in animals, indicate that over 90% of PGE_2 and $PGF_{2\alpha}$ is taken up by the lungs on a single passage through the pulmonary circulation. After two metabolic steps in the lung, the 'lung metabolite' is almost immediately released into the circulation. Uptake by the liver and/or kidney followed by further metabolic degradation results in the excretion of numerous metabolites of the original prostaglandin in the urine and bile.

The enzymatic steps by which the main human urinary metabolite of PGE_2 is produced are illustrated in Figure 2. Oxidation of the 15 hydroxyl by 15-hydroxy prostaglandin dehydrogenase followed by enzymatic reduction of the 13, 14

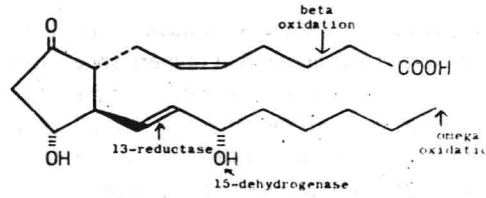

Figure 2 Metabolism of prostaglandin E_2

trans double bond are steps which occur in the lungs especially, although both enzymes are widely distributed throughout the body.

Beta and *omega* oxidation of these lung metabolites occurs principally in the liver. The former causes the loss of 2 or 4 carbons from the alpha (carboxyl) chain, the latter results in oxidation of the terminal methyl group first to an alcohol, then an aldehyde, and finally an acid.

Although these are the most well-documented steps, many variations of them are possible, and human urine contains a large number of different prostaglandin metabolites.

Both TXA_2 and TXB_2 are substrates for the dehydrogenase and the reductase, the resulting lung metabolite is a 13, 14-dihydro-15-oxo-TXB_2. Neither PGI_2 nor PGA_2 is significantly removed on passage through the lungs. On the basis of such evidence it has been suggested by some that one or both of these substances may be a circulating autacoid of the classical hormonal type.

Finally, mention must be made of the 19-hydroxyprostaglandins. These are chemically PGE_1 and PGE_2 with hydroxyl substituents on the penultimate carbon of their *omega* side chain and were first discovered in human seminal plasma. They occur in high concentration in addition to the classical prostaglandins, especially PGE_1 and PGE_2. In non-human primates, however, these 19-hydroxylated prostaglandins appear to be the only prostaglandins present in semen.

Prostaglandins in Obstetrics and Gynaecology

Induction of Labour

In the late 1960's Dr Sultan Karim identified in normal amniotic fluid, umbilical cord, and other fetal tissues substances which were identical to PGE_2 and $PGF_{2\alpha}$ in chromatographic and biological properties. This finding, coupled with the known stimulant action of $PGF_{2\alpha}$ on pregnant human myometrial strips *in vitro*, prompted him to suggest that $PGF_{2\alpha}$ may have a physiological role in the myometrial contractions of human labour. Subsequent research has provided a variety of evidence in favour of such a role. Although its function is still not

precisely defined, there is certainly some solid factual basis to the hypothesis which must be elevated to a status above that of mere speculation.

On the assumption that this hypothesis was correct, the next logical step of an applied nature was for Karim to propose that the physiologically important $PGF_{2\alpha}$ should be useful clinically for the initiation of myometrial contractions at term. He investigated the effects of intravenously infused $PGF_{2\alpha}$ on patients in labour. His results were promising and further investigations were rapidly undertaken by Karim himself and by several other groups, notably in the United Kingdom, Sweden, and the United States. Shortly afterwards, PGE_2 was shown also to be effective in contracting the human myometrium *in vivo*; indeed, it is more potent than $PGF_{2\alpha}$.

Clinical trials were performed at four centres in the United Kingdom and essentially confirmed these early findings. However, $PGF_{2\alpha}$ tends to cause gastrointestinal disturbances whilst PGE_2 produces local vasodilatation or possibly inflammation at the site of infusion if small leakages occur into the interstitial spaces; and, in the larger doses required to induce abortion, PGE_2 also has unwanted effects on the gastrointestinal tract.

A big advance which placed PGE_2 and $PGF_{2\alpha}$ in a very favourable position compared with the long-established oxytocin for the induction of labour, was the discovery that these prostaglandins are active when taken by mouth in capsular form. It is claimed, moreover, that the timing of labour can be predicted within a given number of hours following such PGE_2 administration. Thus, an era of elective induction may have dawned whereby delivery can be planned to occur at a time convenient to all concerned and in particular during the daytime hours rather than during the night.

PGE_2 and oxytocin both continue to have their advocates: for example, in Rh-sensitised mothers, toxaemia of pregnancy, or the presence of cardiovascular disease PGE_2 is probably safer than oxytocin. Moreover, PGE_2 appears less liable to cause uterine 'muscle spasms' which can lead to fetal distress or even rupture of the uterus. On the other hand, some mothers (those with a low score on the Bishop scale) may require such large doses of PGE_2 that its gastrointestinal adverse effects become a significant factor. In such cases, oxytocin may be the drug of choice. As a compromise, there may be a case for the combined use of PGE_2 and oxytocin by intravenous infusion, since the two drugs together appear to be more effective than either alone.

Removal of the dead fetus

Whilst the dead fetus can be allowed to remain *in utero* until full term, and then expelled naturally or with the aid of oxytocin, many pregnant women are upset at the thought of continuing an unsuccessful pregnancy. Indeed, to do so may lead to disorders of a psychological nature. PGE_2 administered as a vaginal pessary is an effective means of expelling such a dead fetus within, on average, 10 hours.

Termination of Pregnancy (abortion)

Karim followed his early clinical success with the induction of labour by a claim that mid-trimester abortions can be produced if sufficiently large doses of $PGF_{2\alpha}$ or PGE_2 are infused intravenously. Since oxytocin is without effect, the only alternative methods for abortion during the mid-trimester are surgery or the injection of hypertonic saline. The mid-pregnant human myometrium is only about one-tenth as sensitive to prostaglandin as the myometrium at term though again the tissue is more sensitive to PGE_2 than $PGF_{2\alpha}$. The pronounced adverse effects of $PGF_{2\alpha}$ (especially vomiting and diarrhoea) have resulted in a universal preference for PGE_2as an abortifacient.

Intravenous infusion is an excellent method for the administration of a new drug when information about the necessary dose, duration of action, and adverse effects is needed. It is a less than suitable route for practical routine use in a busy abortion clinic. The intrauterine route (either intra-amniotic or extra-amniotic) is a direct way of relieving a high concentration of PGE_2 in the region of its target, the myometrial muscle, and such local administration is probably now the method of choice. The record of safety using such a technique for induction of abortion is impressive. Abortion following the intrauterine injection of PGE_2 is also relatively quick, being complete in about 16 hours. However, like spontaneous abortion, prostaglandin-induced abortion, can be extremely painful and distressing to the patient.

It may be noted that expulsion of hydatidiform moles can be achieved very readily by abortifacient doses of PGE_2, using either the intravenous or intra-uterine routes.

Self-administration of prostaglandins by the vaginal route could conceivably form the basis of a 'do-it-yourself' abortion. Pessaries containing PGE_2 (or a synthetic analogue) given at 3-hourly intervals achieve abortion with something like a 95% success-rate. Finally, it should be emphasised that there seems little point in using PGE_2 for first trimester abortions which can be performed very satisfactorily by existing methods, namely, suction or curettage.

Contraception

Since PGE_2 in sufficient dosage is an abortifacient even in very early pregnancy, and since mid-trimester abortions can be successfully induced by prostaglandins given intravaginally, it seems reasonable to presume that the vaginal administration of a suitably potent prostaglandin (possibly a synthetic analogue), as soon as pregnancy is suspected (i.e., after a missed, or late, menstrual period), should result in emptying of the uterine contents. It follows therefore that this procedure may cause either a very early abortion or the induction of a menstrual period which for some reason (other than pregnancy) is late or delayed. The overall result, however, will be the same, and there seems a good prospect for the

development of something akin to the 'morning-after' pill — a method of birth control with many obvious advantages over the widely used oral contraceptive steroids.

Finally, it can be envisaged in the future that the regular, once-monthly, insertion of a vaginal pessary containing a suitable prostaglandin could be used to initiate menstruation in a regular and controlled manner. Such therapy might not be condemned by the anti-abortionists or by others to whom abortion is either an anathema or a truly moral problem. It might, however, be argued that since menstruation is going to occur naturally without such drug administration in most instances, by a mechanism in which endogenous endometrial prostaglandins are implicated, and since excessive prostaglandin production may account for some of the unpleasant symptoms or disorders of menstruation, the use of exogenous prostaglandins in a normally menstruating, non-pregnant woman is not only unnecessary but is likely to cause increased incidence of these menstrual dysfunctions. A possible pharmacological approach to this would be to give a short course of prostaglandin-synthesis-inhibiting drugs, such as indomethacin, some days prior to the expected day of natural menstruation. This would prevent the formation of endogenous prostaglandins whilst the actions of the exogenous prostaglandin, administered simultaneously *per vagina*, would be unimpaired. All menstruation could be artificially induced by means of the pessary, possibly with fewer adverse effects than are experienced under natural conditions if the dosage and the nature of the drugs used were selected wisely. Moreover, within certain limits the day of onset of menstruation could be planned ahead.

Fertility in the Human Male

Human seminal plasma is rich in prostanoids. Indeed, their high concentrations in that fluid was responsible for the original discovery of 'prostaglandin' by pharmacological tests during the 1930's. Since then there has been much interest in their role in the male reproductive tract, but no real progress has been made. Very few species apart from the primates have similarly high levels in their semen or even detectable amounts at all in many instances. This seems to point to some reproductive function which is peculiar to the higher mammals.

The presence of the 19-hydroxy analogues of PGE_1 and PGE_2 in primate semen is possibly unique, but pharmacological studies on these compounds have not yet revealed any activities which might provide a clue as to their biological role.

There is some evidence that certain infertile males have lower than normal levels of PGE compounds. It would be of great interest to know whether their fertility could be restored by prostanoid replacement therapy, if a feasible means of administration could be devised.