Prostaglandins in Reproduction

Norman L. Poyser

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Norman L. Poyser, B. Pharm., Ph.D.

Department of Pharmacology
University of Edinburgh, Scotland

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Prostaglandins in Reproduction

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   Norman L. Poyser

Foreword

A less than cursory glance at the Index Medicus will provide ample evidence of the popularity, if not importance, of the prostaglandins as subjects of scientific research throughout biology. These fatty acid derivatives appear to be ubiquitous and omnipotent - indeed it is a mark of distinction for a cell to be unable to synthesize or respond to prostaglandins.

As the prostaglandins were first discovered in semen, it is very appropriate that this first monograph in the series should deal with Prostaglandins and Reproduction. The early inference that prostaglandins had some part to play in the processes of reproduction has been, and is still being, fully justified by direct experiment. If we had conceived the control mechanisms for reproduction only in terms of steroids and peptide hormones, the last 25 years would have forced us to reconsider those mechanisms to include the prostaglandins. Their influence is felt at all stages, from the release of hormone releasing factors to the closure of the ductus arteriosus in the first days of life. In some species they are the prime movers of essential events, in others they are important modulators of the effects of steroids or peptides.

Norman Poyser is ideally qualified to guide the reader through the seeming maze of correlations and connections between the prostaglandins, steroids and peptides concerned with reproductive functions. He has made no attempt to gloss over the contradictions and unanswered questions that are the hallmark of an active research field and his lucid presentation of facts and hypotheses in this monograph will undoubtedly enlighten our understanding of the place of Prostaglandins in Reproduction.

Y. S. Bakhle

London

Preface

The word "prostaglandin" was introduced into the scientific literature by Professor U.S. von Euler in 1935 as a name for an acidic lipid found in human semen. Since that time, the number of prostaglandins described has increased tremendously. This monograph is not, however, about the reproduction of prostaglandins. It attempts to describe the importance of prostaglandins in various reproductive processes. The writing of this monograph has meant reading a very large number of references, but what percentage of the relevant published literature I have actually scanned is difficult to estimate. I hope this percentage is high so that there are not too many glaring omissions. I have tried to arrive at objective conclusions concerning the roles of prostaglandins in reproduction but, in a monograph of this nature, some subjective opinions are bound to arise. Each chapter is as fully referenced as possible (but, due to lack of space, not all references on a particular topic can be given) in order that material sources may be followed up in greater depth if required.

I have tried to aim this monograph for scientists who are interested in reproduction and wish to know where prostaglandins fit into this field, and for those scientists who are interested in prostaglandins and wish to know what roles these substances have in reproduction. I hope I have succeeded. Prostaglandins, like steroids, include many compounds with very similar structures but with very different actions so, to the scientist not readily conversant with the nomenclature, the prostaglandin field seems complex. To briefly clarify the situation, prostaglandins are identified by giving them a letter from A to I together with a subscript from 1 to 3. Prostaglandin (PG) F can also be α or β, and this refers to the position of the hydroxyl group attached to the number 9 carbon atom, i.e. the one at the top of the five-membered carbon ring. Thromboxanes have an additional oxygen atom enclosed in the ring. The potential number of compounds is quite large, although the number relevant to reproduction is small. With one

exception (see Chapter 2), only the 2-series prostaglandins are physiologically important since their precursor, arachidonic acid, is present in the tissues in far greater amounts than the fatty acids which form the precursors of the 1- or 3- series prostaglandins. In addition, most studies in reproduction have involved using or measuring PGE_2 and $PGF_{2\alpha}$. PGE_1 and $PGF_{1\alpha}$ have essentially similar qualitative actions but, whereas PGE_1 is usually similar to or slightly less potent than PGE_2, $PGF_{1\alpha}$ is usually much less potent than $PGF_{2\alpha}$. The amount of information involving prostacyclin (PGI_2) and the thromboxanes in reproduction is relatively small. It is doubtful whether the unstable endoperoxides, PGG_2 and PGH_2, are involved except as precursors for the other prostaglandins and for the thromboxanes. However, to actually prove that a particular prostaglandin is an essential link in a reproductive process is quite difficult since prostaglandins are often produced and act locally. In spite of these difficulties, I hope this monograph helps clarify those areas in reproduction in which prostaglandins are important.

Finally, I would like to express my gratitude to Dr. E.W. Horton who, 12 years ago, gave me the opportunity to work in the prostaglandin field, and for the encouragement he has given me over the years. Concerning the monograph, I wish to thank the authors of papers and editors of journals who gave me permission to reproduce their figures and tables, Dr. Y. Bakhle for editing the original manuscript, my wife Valerie for sorting out the references, and especially Miss Moira Dickson and Mrs. Susan Waugh for performing the difficult task of typing the monograph in a camera-ready form.

N.L. Poyser
December, 1980

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CHAPTER 1
Prostaglandins

An Introduction

Prostaglandins have always been connected with reproduction, as they were originally discovered in human seminal plasma. They were thought to be produced by the prostate gland, hence their name, though subsequently it was found that the seminal vesicles were the source of the prostaglandins in seminal plasma (4). The structures of the 2-series prostaglandins are shown in figure 1. Prostaglandins are 20 carbon-containing fatty acids, consisting of a cyclopentane ring to which is attached two chains, termed α and ω, containing 7 and 8 carbon atoms, respectively. Numbering of the molecule starts at the carbon in the carboxyl group on the α chain, so that the hydroxyl group on the ω chain is at position 15. Thromboxanes are distinguished from prostaglandins by the fact that they have an additional oxygen atom in the ring. The stereochemistry of the different structures is shown.

Prostaglandins of the 2-series are formed from arachidonic acid (10,3). It is first converted to PGG_2, and this step can be inhibited by the aspirin-like drugs. PGG_2 can break down into PGH_2 and these two endoperoxides may be converted to PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 and TXA_2. PGI_2 and TXA_2 are unstable in body fluids and readily form 6-oxo-$PGF_{1\alpha}$ and TXB_2

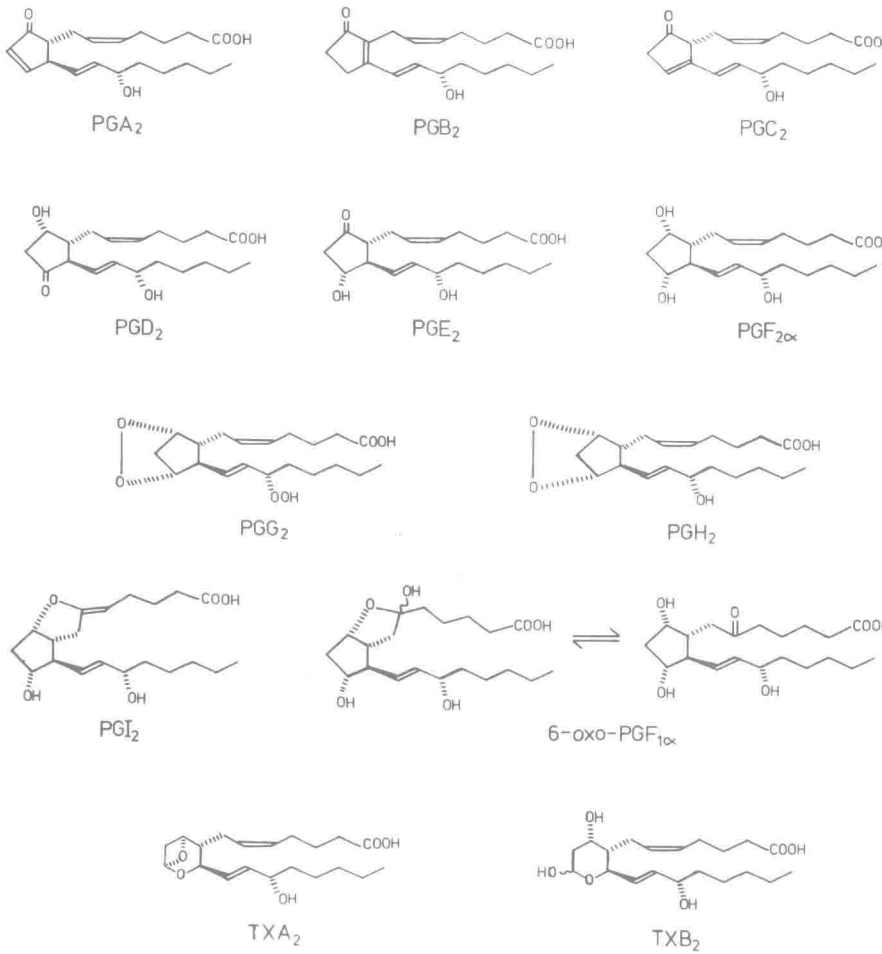

Fig. 1. Prostaglandins of the 2-series: Chemical structures.

respectively, with a consequent large loss in biological activity. PGE_2 in acidic conditions dehydrates to form PGA_2, and this can be isomerised enzymatically into PGG_2, then PGB_2 (9). Treatment of PGE_2 with base converts it directly to PGB_2. 19-Hydoxylated derivatives of PGE_2, $PGF_{2\alpha}$, PGA_2 and PGB_2 have also been found.

Prostaglandins and thromboxanes of the 1-series do not possess the 5,6-double bond. PGI_1 cannot be formed naturally. The precursor of the 1-series is ω-dihomo-γ-linolenic acid. Prostaglandins of the 3-series have an extra 17, 18 trans double bond compared with the 2-series prostaglandins. They are formed from 5,8,11,14, 17-eicosapentaenoic acid.

Prostaglandins are metabolized at the 15-position by oxidation of the secondary alcohol group into a ketone. NAD^+ is required as co-factor. The 15-oxo-prostaglandins so formed, especially of the F series, may not lose much biological activity when compared with the parent compound. Subsequent reduction of the 13,14-double bond results in a much larger loss in biological activity. The 13,14-dihydro-15-oxo-prostaglandins formed are the main circulating metabolites of PGE_2 and $PGF_{2\alpha}$ and may exceed the plasma levels of the primary prostaglandins by some 20-fold. Most tissues can carry out these transformations, to a greater or lesser extent, and some tissues, e.g. lungs, have very high metabolic activity (10,12). 95-99% of PGE_2 or $PGF_{2\alpha}$ present in the circulation is removed by one passage of the blood through the lungs (5). It is doubtful therefore whether PGE_2 and $PGF_{2\alpha}$ can act as circulating hormones. Measuring the levels of these prostaglandins in peripheral plasma is pointless when release from a particular organ is being examined. However, useful information can be obtained concerning the release of $PGF_{2\alpha}$ by measuring the levels of its 13,14-dihydro-15-oxo-metabolite The equivalent metabolite of PGE_2 is not so useful as it readily dehydrates into the PGA_2 metabolite making measurement difficult.

PGA_2, although a good substrate for the metabolising enzymes, escapes removal from the circulation when passing through the lungs (8). This would indicate that PGA_2 is not a substrate for the uptake process in the lungs (3). Similarly, PGI_2 and 6-oxo-$PGF_{1\alpha}$ escape degradation by the lung (6), so PGI_2 (half-life 3-5 min) may act as a circulating hormone. TXA_2 has a half-life of only 30 seconds so whether it is taken up by the lungs and metabolised is not known. It is unlikely to act as a circulating hormone.

The main circulating metabolites of prostaglandins are metabolised further in the liver to dinor and tetranor compounds by β-oxidation, and by ω-oxidation into the 20 alcohols or carboxylic acids. Hydroxylation at the 19-position can also occur; and PGE compounds may be converted to PGF derivatives. Consequently, many urinary metabolites may result from any one prostaglandin, and the main metabolite produced depends upon the species (7, 12).

PGI_2, although not taken up and metabolised by the lungs, is still oxidised at the 15 position with the ultimate production of 6,15-diketo-13.14-dihydro-$PGF_{1\alpha}$. Attack on the α- and ω-chains by β- and ω-oxidation also occurs (11, 14). PGI_2 is metabolised enzymatically before it degrades non-enzymatically into 6-oxo-$PGF_{1\alpha}$, although some of this latter substance is formed. 6-oxo-$PGF_{1\alpha}$ is a poorer substrate than PGI_2 for the 15-hydroxy-prostaglandin dehydrogenase enzyme although its metabolic pathway in the body is qualitatively similar to PGI_2 (15).

Prostaglandins are not stored in tissues. They are synthesised and released, as required. Whether release from and across cell is passive or by active transport is under investigation (1, 2). Arachidonic acid is by far the most abundant unsaturated fatty acid in most cells, so prostaglandins of the 2-series are predominantly formed. The levels of free arachidonic acid in tissues are usually too low for prostaglandin synthesis to occur. Arachidonic acid has therefore to be released from some bound

source, and phospholipids are commonly regarded as providing this bound pool of arachidonic acid. It is released by the action of the enzyme, phospholipase A_2. Activation of this enzyme would appear essential by any stimulus for prostaglandin release. Cell damage or death readily activates this enzyme, so prostaglandins are readily formed by such cells. This must be taken into account when tissues are removed for measuring prostaglandin content.

Prostaglandins are probably formed and act locally though passage from one organ to another does take place in certain instances, as described later. Prostaglandins as mediators of biological activity are fairly unusual in so far as every tissue in the body has the capacity to synthesise them. Whether all tissues actually do synthesise prostaglandins, in vivo, is not known. However, the next 6 chapters deal with the importance of prostaglandin production by reproductive organs. Chapter 8 deals with the mechanism of prostaglandin synthesis by such tissues, while the last chapter outlines the use of prostaglandins and prostaglandin synthetase inhibitors in clinical and veterinary practice.