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E. W. Horton
Prostaglandins

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Preface

This book was written at the invitation of Dr. H. Götze of Springer-Verlag for the series "Monographs in Endocrinology". It is not a comprehensive account of the prostaglandins but has been written with a deliberate emphasis upon those aspects of the field in which I am particularly interested and to which, in some cases, I have made a contribution.

I am grateful to Miss E. Pfisterer and her colleagues of Springer-Verlag for their excellent work. I should also like to thank my wife without whose patience, encouragement and help this book would never have been completed.

Finally this is an appropriate time to express my sincere gratitude to those scientists who over the years have given me samples of prostaglandins—namely Professors S. Bergström and B. Samuelsson of the Karolinska Institute, Stockholm, Professor D. A. van Dorp of the Unilever Research Laboratories, Vlaardingen and Dr. J. E. Pike of the Upjohn Company, Kalamazoo. Without their help work in this field would have been extremely difficult.

E. W. H.

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I. Introduction

1. Discovery of Prostaglandin

The credit for the discovery of the prostaglandins rightly belongs to the Swedish scientist, U. S. VON EULER. It is true that other workers had observed pharmacological effects with semen and prostatic extracts which can now, with hindsight, be attributed to the presence of prostaglandins (for example BATTEZ and BOULET, 1913; KURZROK and LIEB, 1930; COCKRILL, MILLER and KURZROK, 1935; GOLDBLATT, 1933, 1935), but it was VON EULER (1934, 1935 a, 1936, 1939) who established beyond doubt that the active principle, which he named prostaglandin, belongs to a completely new group of naturally occurring substances; furthermore, it was at VON EULER's suggestion that Professor SUNE BERGSTRÖM in 1947 took up the problem of prostaglandin purification. This led to the isolation of the first two prostaglandins in 1960 and so a vast new field of chemical, biological and clinical importance was opened up.

VON EULER (1934) observed that human semen and extracts of sheep vesicular glands lower arterial blood pressure on intravenous injection and stimulate various isolated intestinal and uterine smooth muscle preparations. He showed that the active principle, prostaglandin, was a lipid soluble acid and thus differed chemically from all other known subtances with similar biological activity, for example, histamine, acetylcholine and adenylic compounds (VON EULER, 1935 a, 1936). GOLDBLATT (1935) independently distinguished the active principle also from substance P. VON EULER made use of prostaglandin's physico-chemical properties in preparing an extract for further biological work. He extracted sheep vesicular glands with ethanol and after evaporation to dryness, partitioned the residue between ether and water at acid and alkaline pH. This partially purified prostaglandin (PG) was stable for many years.

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2. Pharmacological Properties

PG lowered the systemic arterial blood pressure of the urethanised rabbit on intravenous injection (VON EULER, 1935 a). It had little or no action on the isolated perfused heart of the rabbit, but increased flow through the perfused hind limb and kidney and decreased flow through the pulmonary vascular bed (VON EULER, 1939). It thus seemed likely that the depressor action of PG in the rabbit could be attributed to changes in vascular resistance rather than to an effect upon the heart. Pressor responses to adrenaline were also reduced by PG.

VON EULER (1939) observed that the depressor response to PG was more rapid in onset after an injection into the femoral vein than after an injection into the femoral artery, suggesting the possibility of a site of action in addition to a direct vasodilator effect on the hind limb. Injection into the cat portal vein increased portal venous pressure and decreased systemic arterial pressure. There was also decreased flow on injection of PG into the perfused cat kidney. On the cat heart-lung preparation PG had little action (VON EULER, 1939).

Other cardiovascular effects of PG observed at that time were its constrictor action on the perfused human placental vessels (VON EULER, 1938) and its positive inotropic and chronotropic effects on the isolated frog heart.

Prostrate, seminal vesicles and seminal fluid of the Rhesus monkey contain a depressor substance which lacks the smooth muscle stimulating activity of PG. VON EULER (1935 b) named the active principle, vesiglandin. Tissues and organs of several species were tested for PG-like activity (VON EULER and HAMMARSTRÖM, 1937). Some activity was found in the ovary. However, in no organ could PG be detected in a concentration approaching that found in human seminal plasma.

3. Prostaglandin and Reproduction

ELIASSON and his colleagues working in VON EULER's laboratory made several important contributions to the role of PG in reproductive physiology. ELIASSON (1959) confirmed that PG, like human semen, inhibits the spontaneous contractions of isolated myometrial strips from the non-pregnant woman and showed that the preparation

is most sensitive at the time of ovulation (BYGDEMAN and ELIASSON, 1963). ELIASSON and POSSE (1960) found that PG administered intravaginally stimulates contractions of the non-pregnant human uterus at the time of ovulation. ELIASSON (1957) established by making comparisons on various biological preparations that the PG from human seminal fluid was similar to that in the sheep vesicular gland. He also observed that when minced sheep vesicular glands were incubated in phosphate buffer at 37°, their PG content increased 10-fold in a few minutes. Furthermore the amount formed could be increased by the addition of phospholipase A. Incubation of human seminal fluid with or without enzyme did not increase the yields of prostaglandins (ELIASSON, 1959).

Finally, ELIASSON (1959) made the important observation, by fractionation of ejaculates, that human seminal PG is secreted mainly by the seminal vesicles not by the prostate. Thus the original assumption which gave rise to the name, prostaglandin, was proved incorrect. By that time however, pure prostaglandins were being isolated and the name soon became established in the literature.

4. Isolation and Structure

The impetus for further biological work resulted from the elegant isolation and chemical characterisation achieved by BERGSTRÖM, SJÖVALL, SAMUELSSON and their co-workers at the Karolinska Institute. BERGSTRÖM and SJÖVALL (1960 a, b) isolated two compounds which behaved differently on partition between ether and an aqueous phosphate buffer. The one more soluble in ether was called prostaglandin E (PGE), the other more soluble in phosphate buffer (in Swedish spelt with an "F") was called prostaglandin F (PGF). These compounds were assigned the empirical formulae $C_{20}H_{34}O_5$ and $C_{20}H_{36}O_5$ respectively.

It was soon discovered that unsaturated analogues of these prostaglandins are present in human semen and in other tissues, notably the lungs.

In 1962 and 1963 BERGSTRÖM and his co-workers announced the chemical structure of several naturally occurring prostaglandins (BERGSTRÖM, RYHAGE, SAMUELSSON and SJÖVALL, 1963). Since then research in this field has advanced rapidly.

5. Prostaglandin-like Substances

In the meantime, other workers had discovered smooth muscle stimulating lipids in numerous tissues. Frog intestine spontaneously releases darmstoff (VOGT, 1949). Rabbit iris contains irin (AMBACHE, 1957, 1959) which may be the chemical mediator responsible for the atropine-resistant miosis resulting from antidromic stimulation of the trigeminal nerve. The menstrual stimulants are a group of lipids extracted from human menstrual fluid (PICKLES, 1957). Several workers have reported the presence of smooth muscle-stimulating lipids in the brain (AMBACHE and REYNOLDS, 1960, 1961; KIRSCHNER and VOGT, 1961; TOH, 1963). LEE, COVINO, TAKMAN and SMITH (1965) published a paper on the depressor lipid in rabbit kidney medulla, which they called medullin. All these substances are lipid soluble, all behave like organic acids and all have pharmacological actions on smooth muscle.

Recent work suggests that the presence of one or more prostaglandins can account for much if not all the biological activity of frog darmstoff (VOGT, SUZUKI and BABILLI, 1966), human menstrual fluid (EGLINTON, RAPHAEL, SMITH, HALL and PICKLES, 1963), sheep iris extracts (ÄNGGÅRD and SAMUELSSON, 1963), ox brain lipids (SAMUELSSON, 1964) and medullin (LEE, CROWSHAW, TAKMAN, ATTREP and GOUGOUTAS, 1967).

6. Nomenclature

The basic 20-carbon skeleton of the prostaglandins has been named prostanoic acid (Fig. 1). The correct chemical name of all prostaglandins, their metabolites and analogues can be derived by refer-

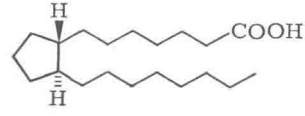


Fig. 1. Prostanoic acid

ence to this structural formula. These chemical names although precise are long and tedious to use; for the major prostaglandins trivial names have been retained.

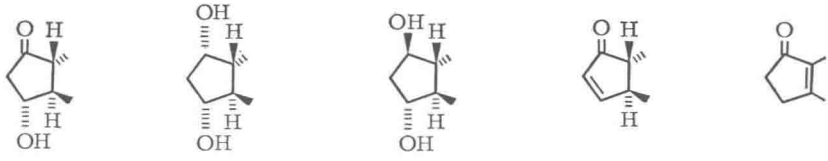
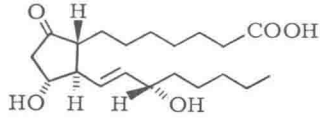
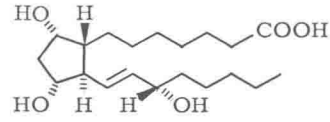
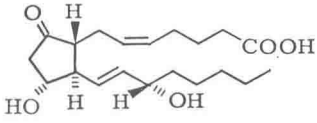
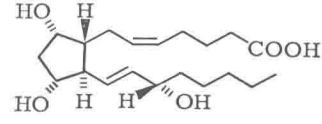


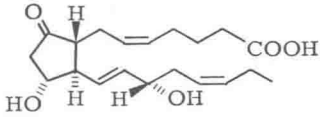
Fig. 2. Structural differences between prostaglandins of the E, F, A and B series

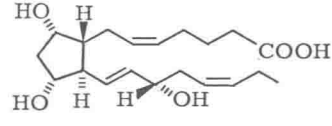


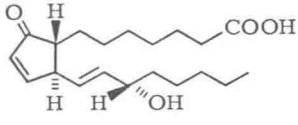


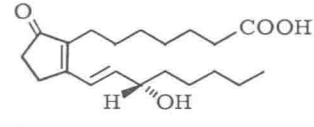


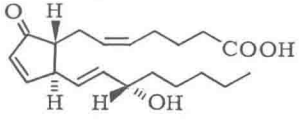












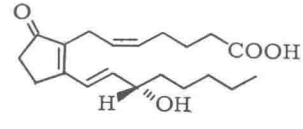


Fig. 3

Four series of natural prostaglandins have so far been described, designated by the letters E, F, A and B corresponding to differences in the five membered ring (Fig. 2). All the "primary" prostaglandins (Fig. 3) are hydroxylated in the 15 position and contain a 13, 14-*trans* double bond. The degree of unsaturation of the side chains is indicated by the subscript numeral after the letter, thus prostaglandins E_1, F_1,

Table 1. *Names and designations of some prostaglandins* (see Fig. 3 for structural formulae)

Trivial name	*Abbreviation (used in this book)*	*Chemical name*	*Andersen's designation*
Prostaglandin E_1	PGE_1	11α,15α-dihydroxy-9-oxo-13-*trans*-prostenoic acid	PG $(E\alpha\alpha)_1$
Prostaglandin E_2	PGE_2	11α,15α-dihydroxy-9-oxo-5-*cis*-13-*trans*-prostadienoic acid	PG $(E\alpha\alpha)_2$
Prostaglandin $F_{1\alpha}$	$PGF_{1\alpha}$	9α,11α,15α-trihydroxy-13-*trans*-prostenoic acid	PG $(\alpha\alpha\alpha)_1$
Prostaglandin $F_{1\beta}$	$PGF_{1\beta}$	9β,11α,15α-trihydroxy-13-*trans*-prostenoic acid	PG $(\beta\alpha\alpha)_1$
Prostaglandin $F_{2\alpha}$	$PGF_{2\alpha}$	9α,11α,15α-trihydroxy-5-*cis*-13-*trans*-prostadienoic acid	PG $(\alpha\alpha\alpha)_2$
Prostaglandin A_1	PGA_1	15α-hydroxy-9-oxo-10,13-*trans*-prostadienoic acid	PG $(A\Delta\alpha)_1$
Prostaglandin B_1	PGB_1	15α-hydroxy-9-oxo-8 (12),13-*trans*-prostadienoic acid	PG $(B\text{-}\alpha)_1$

Footnote On Andersen's designation. Configurations at C-9, C-11 and C-15 are indicated, in that order, by α or β within parentheses. Subscripts indicate the degree of unsaturation in the corresponding E-type prostaglandin. When no configuration assignment is required, the designations are: K = oxo, Δ = double bond, and — (dash) for no substituent. In 9-oxo compounds E, A or B replaces K. Prostaglandins with *cis*-orientated side chains are designated by prefixing iso-to the abbreviation used for the C-8 epimer. The antipodes and racemates are designated by the prefixes ent- and rac- respectively.

A_1 and B_1 have only the *trans* double bond, prostaglandins E_2, F_2, A_2 and B_2 have in addition, a *cis* double bond in the 5, 6 position while prostaglandins E_3, F_3 and B_3 have an additional *cis* double bond in the 17, 18 position. Chemical reduction of a prostaglandin E yields two isomeric alcohols F α and F β.

In this monograph prostaglandins will be referred to where possible by an abbreviation e. g., PGE_1, $PGF_{2\alpha}$, PGB_3, etc. (see Table 1). Where ambiguity might occur the full chemical name is used.

An alternative system of abbreviations which takes into account stereochemical configurations has been introduced by ANDERSEN (1969). This new designation is useful when discussing the effects of stereochemical changes upon pharmacological activity or chromatographic behaviour. The essential features are described in the footnote to Table 1, but the system will not be used in this monograph.

7. Prostaglandin Literature

Well over a thousand papers have now been published on various aspects of prostaglandin research. Many are not referred to in this book. For those readers who wish to keep abreast of this rapidly expanding literature, the prostaglandin bibliography prepared and published by the Upjohn Company, Kalamazoo, is invaluable. Recent reviews have been written by BERGSTRÖM (1967), BERGSTRÖM, CARLSON and WEEKS (1968), VON EULER and ELIASSON (1967), HINMAN (1967), PICKLES (1967, 1969), VON EULER (1968), HORTON (1968, 1969), RAMWELL and SHAW (1970) and RAMWELL, SHAW, CLARKE, GROSTIC, KAISER and PIKE (1968).

Earlier literature has been reviewed by VOGT (1958), ELIASSON (1959) and VON EULER (1966). The proceedings of several symposia have been published (PICKLES and FITZPATRICK, 1966; BERGSTRÖM and SAMUELSSON, 1967; RAMWELL and SHAW, 1968, 1971; MANTEGAZZA and HORTON, 1969).

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