THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 67:650–653, 1976

Vol. 67, No. 5, Part 2 of 2 parts
Printed in U.S.A.

THE PROSTAGLANDINS

JOHN E. PIKE, PH.D.

Experimental Chemistry Research, The Upjohn Company, Kalamazoo, Michigan, U. S. A.

The prostaglandins (PGs) are a family of naturally occurring, humoral agents characterized by a unique, oxygenated, low-molecular-weight, fatty acid structure incorporating a 5-membered ring (for general references see [1–9]). Examples of the structures of some of the more important prostaglandins are shown in Figure 1. Since their original discovery in the 1930s and the much later elucidation of the structure of the purified prostaglandins by Bergstrom and his collaborators at the Karolinska Institute, several developments have been of special significance. First and most striking is the large number of structural variations within the prostanoid family, which has now expanded from the first known PGE and PGF stuctures to include the PGAs, PGBs, PGCs and PGDs, and to this structural diversity one must add the unique biologic properties associated with each type of molecular modification. Biologic testing of the prostaglandins has uncovered a wide variety of pharmacologic activities in a large number of areas and this has led to some possible clinical uses for the natural compounds and their analogs (Tab. I)

The prostaglandins are formed by nearly all cells from membrane-located stores of polyunsaturated acids bound as phospholipids, and the biologic effects of these agents are characteristically seen at extremely low concentrations (10^{-9} gm/ml), making them among the most potent, naturally occurring substances. Another important theme of the ongoing research in this area has been the elucidation of the details of the biosynthesis and metabolism of these agents. In addition to the structural characterization of the metabolites, it seems now well established that the prostaglandins are locally active in tissues and are inactivated rapidly by prostaglandin-specific enzymes located close to their sites of formation. One can, therefore, think of prostaglandins as "local" hormones or autacoids.

Research to date has been less successful in answering two more fundamental questions: What is the role for prostaglandins in normal body function or in disease states? Why are the prostaglandins so widely distributed with such apparently diverse effects? Suggestions for possible physiologic roles or involvement in pathologic states (Tabs. II, III) do little to answer or clarify these questions.

One approach to thinking about prostaglandins has been to see their role as part of an overall system (Fig. 2) which encompasses their formation from phospholipids and subsequent metabolism and inactivation [10]. Each enzymatic step in this sequence is a control point which can be either stimulated or inhibited, and to date we know little of the natural mechanisms that regulate these processes. One thought-provoking idea proposed by Vane [11] is that the mechanism of action of nonsteroidal anti-inflammatory agents (such as aspirin and indomethacin) is the inhibition of the biosynthesis of prostaglandins. Of course, this is only one potential control point and one would anticipate that other pharmacologic agents could owe their actions, at least in part, to effects on some of these enzymatic steps. The various intermediates in the pathways would be expected to

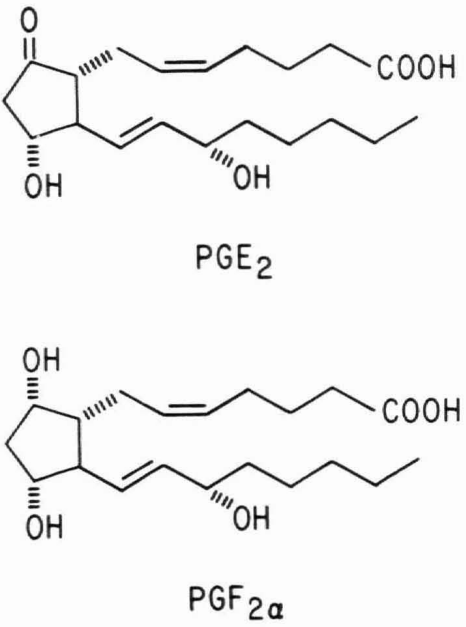

FIG. 1. Prostaglandin E_2 and $F_{2\alpha}$ structures.

Reprint requests to: Dr. J. E. Pike, Experimental Chemistry Research, The Upjohn Company, Kalamazoo, Michigan 49001.

Abbreviations:
HETE: 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid
HHT: 12-hydroxy-8, 10-heptadecadienoic acid
HPETE: hydroperoxide of 12-L-hydroxy-5,8,10,14- -eicosatetraenoic acid.
PG: prostaglandin
RCS: rabbit aorta-constricting substance

TABLE I. *Potential prostaglandin applications*

Labor induction
Asthma
Hypertension
Clot inhibition
Nasal decongestant
Abortion
Menstrual regulation
Male infertility
Blood platelet preservation
Duodenal ulcers

TABLE II. *Possible physiologic roles for prostaglandins*

Feedback inhibition of neurotransmission
Luteolysis
Labor induction
Closure of ductus arteriosus
Renal autoregulation
Sperm transport
Ova transport

TABLE III. *Possible involvement of prostaglandins in pathologic states*

Inflammation	Contact allergic eczema
Cholera	Male sub-fertility
Psoriasis	Asthma
Carcinoid tumors	Toxemia of pregnancy
Burns	Sickling phenomenon
Hypertension	(Hypercalcemia of sarcomas)
Abortion	Periodontal disease
Uveitis	Fever
Dysmenorrhea	

have unique biologic functions as do the prostaglandins themselves.

Recent studies, especially by Samuelsson, Hamberg and their collaborators [12-16] in Stockholm, have concentrated on the biosynthetic pathway which leads from the polyunsaturated fatty acids to what we might call the classical prostaglandins, and this has led to the isolation and identification of new intermediates in this pathway and to some important revisions of our understanding of the elements of the prostaglandin system.

Early mechanistic studies using homogenates of sheep seminal vesicular glands indicated that the two oxygen atoms of the 5-membered ring of PGE_1 were derived from the same oxygen molecule, lending support to the idea that an endoperoxide intermediate was formed prior to the elaboration of the characteristic prostaglandin structure. This was also supported by the isolation of 12-hydroxy-8,10-heptadecadienoic acid (HHT) and malonaldehyde which could be rationalized chemically as degradation products of the endoperoxide (Fig. 3). Later, two endoperoxides were isolated from short-term incubations of arachidonic acid in the presence of *p*-mercuribenzoate, and these were named PGG_2 and PGH_2. In aqueous buffer (pH 7.4) at 37°C the half-life of these unstable intermediates was about 5 min. They were found to have very significant and potent biologic properties, causing rapid and irreversible aggregation of washed human platelets, and the contraction of respiratory and vascular smooth muscle. In certain in vitro assays they were reported to have as much at 200 times the activity of the corresponding PGE_2 or $PGF_{2\alpha}$. For example, these two intermediates are more potent and faster in onset than PGE_2 in contracting the isolated umbilical artery [17].

In addition to compounds derived from endoper-

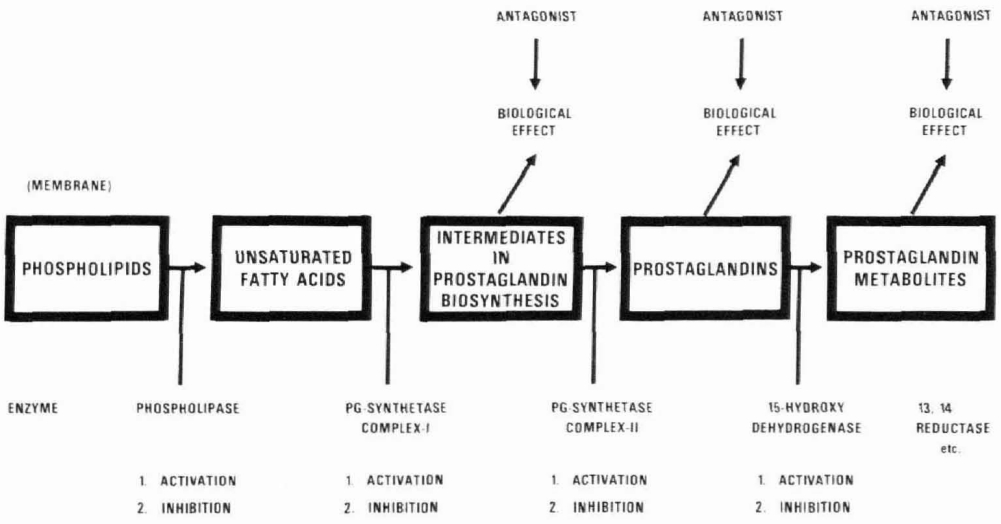

FIG. 2. The prostaglandin system.

endoperoxides, another lipooxygenase type pathway was discovered using platelets. This pathway led from arachidonic acid to 12-L-hydroxy-5,8,10,14-eicosatetraenoic acid (HETE) via the corresponding hydroperoxide (HPETE). Interestingly, this pathway leading from arachidonic acid to HETE is not inhibited by aspirin or indomethacin, but is blocked by the acetylenic counterpart of arachidonic acid, 5,8,11-14-eicosatetraynoic acid. In addition to HHT and HETE, the suspensions of washed human platelets produced a hemiacetal derivative of 8-(1-hydroxy-3-oxopropyl)-9,12-L-dihydroxy-5,10-heptadecadienoic acid, earlier called PHD, but later named thromboxane B_2 (Fig. 4). Hamburg and co-workers [16,18] showed that when washed human platelets were treated with thrombin, these 3 metabolites were produced in much larger amounts than the corresponding classical prostaglandins, and clearly this enzymatic pathway which converts the endoperoxides to these newer metabolites is of major importance in platelets. In an investigation of the transformation of PGG_2 into the hemiacetal thromboxane B_2, evidence was also found for a short-lived intermediate (half-life of only about 30 sec) which could be trapped in the presence of nucleophilic reagents. A structure (Fig. 5) was proposed for this new intermediate which was called thromboxane A_2. It is believed that a major part of the activity of the rabbit aorta-constricting substance (RCS), first described by Piper and Vane, is due to thromboxane A_2. Measurements of these new metabolites have also been made on the perfusates of guinea-pig lung. Injection of arachidonic acid (30 μg)

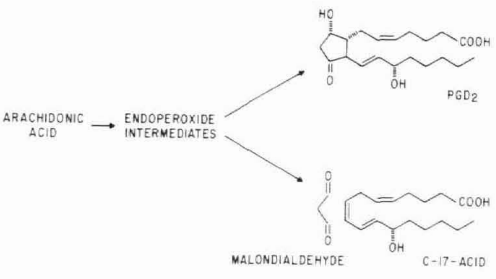

FIG. 3. Metabolism of the prostaglandin-endoperoxides.

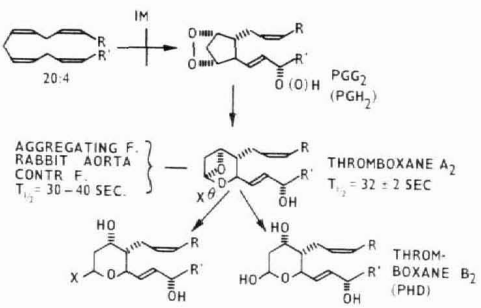

FIG. 5. Thromboxane intermediates.

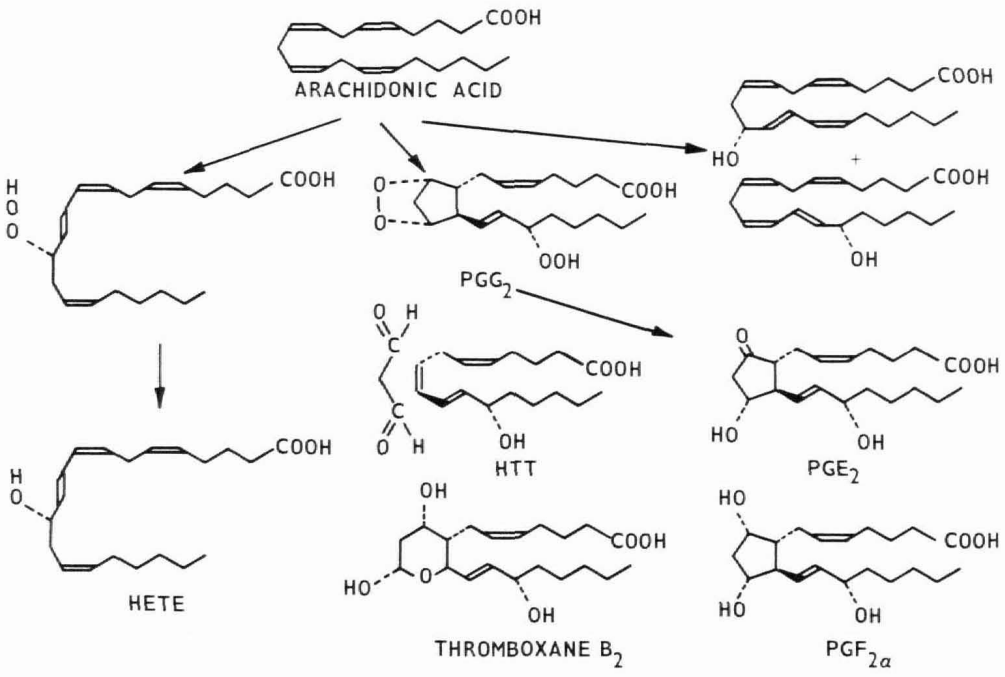

FIG. 4. Arachidonic acid metabolism-thromboxane pathway.

causes the release of thromboxane B_2 (654–2304 ng), HHT (192–387 ng), HETE (66–111 ng), PGE_2 (15–93 gm), and $PGF_{2\alpha}$ (93–171 ng) [19]. While the levels of PGE_2 and $PGF_{2\alpha}$ may be low because of substantial metabolism to the corresponding 15-keto compounds, it is, nevertheless, clear, that the new pathway represents a major metabolic route and the amounts of thromboxane B_2 formed are especially striking. These studies suggest strongly that the thromboxanes have a role in the respiratory system and in anaphylactic reactions.

It will be important to determine whether these newer intermediates, the endoperoxides and their metabolites, have special significance in other cells. Also, it will be interesting to see how important is the biosynthetic pathway to another series of cyclic ethers described earlier by Pace-Asciak and Wolfe [20]. In the stomach where these agents were first discovered, this biosynthetic conversion of arachidonic acid may be a major route. Already a report has appeared which documents high levels of HETE in psoriatic tissue relative to uninvolved skin. These structures pose an unusual challenge for chemical synthesis, especially for those compounds which are relatively unstable. To date, no reports have yet appeared of the synthesis of PGG_2 and PGH_2. One chemical approach to this area by Bundy at Upjohn has been the synthesis of structural analogs of PGH_2 in which each of the oxygen atoms attached to C-9 or C-11 in the endoperoxide structure has been replaced by a methylene (CH_2) group [21]. These compounds are very stable chemically and can be used as models of the natural agents. Like PGH_2, both ethers are powerful constrictors of smooth muscle in vitro and also cause platelet aggregation. Especially remarkable is their activity on bronchopulmonary dynamics in the spontaneously ventilated, pentobarbital-anesthetized dog where they exhibit dramatic constrictor properties.

The recent studies on the biosynthetic aspects of the prostaglandin systems have led to a significant rethinking of some of the earlier ideas. First, one must consider the likelihood that biologic activities, resulting from the initiation of the pathway from arachidonic acid, are due not only to the prostaglandins, but rather to these newer "pre-primary" prostaglandins and their metabolites, which may in certain systems represent a major pathway. Also, pharmacologic agents such as aspirin may owe their activity not to an inhibition of the biosynthesis of prostaglandins themselves, but rather to their ability to prevent the production of the newer endoperoxides or thromboxanes.

REFERENCES

1. Bergström S (ed): International Conference on Prostaglandins, vol 9 of Advances in the Biosciences. Vieweg, Braunschweig, Pergamon, 1973
2. Cuthbert MF (ed): The Prostaglandins. Pharmacological and Therapeutic Advances. London, Heinemann, 1973
3. Horton EW: Prostaglandins, vol 7 of Monographs on Endocrinology. New York, Heidelberg, Berlin, Springer-Verlag, 1972
4. Karim SMM (ed): The Prostaglandins: Progress in Research. Oxford, MTP, Medical and Technical Publishing Co, 1972
5. Lee JB: Prospectives on the Prostaglandins. New York, Medcom, 1973
6. Pike JE: Sci Am 225:84 1971
7. Ramwell PW (ed): The Prostaglandins, vols 1, 2. New York, Plenum, 1973, 1974
8. Robinson HJ, Vane JR (eds): Prostaglandin Synthetase Inhibitors. New York, Raven, 1974
9. Wilson DE (ed): Symposium on Biological Aspects of Prostaglandins. Arch Intern Med 133:29, 1974
10. Pike JE: *In* Proceedings of the Geneva 1973 XII International Therapeutic Union. Geneva, Medecine et Hygiene Publishers, 1974
11. Vane JR: Hosp Prac 7:61, 1972
12. Hamberg M, Samuelsson B: Proc Natl Acad Sci USA 70:899, 1973
13. Hamberg M, Svensson J, Wakabayashi T, Samuelsson B: Proc Natl Acad Sci USA 71:345, 1974
14. Nugteren DH, Hazelhof E: Biochim Biophys Acta 326:448, 1973
15. Hamberg M, Hedqvist P, Strandberg K, Svensson J, Samuelsson B: Life Sci 16:451, 1975
16. Hamberg M, Svensson J, Samuelsson B: Proceedings of the International Symposium on Prostaglandins, Florence, May 1975
17. Tvemo G, Strandberg K, Hamberg M, Samuelsson B: Pediatr Res 8:908, 1974
18. Hamberg M, Svensson J, Samuelsson B: Proc Natl Acad Sci USA 72:2994, 1975
19. Hamberg M, Samuelsson B: Biochem Biophys Res Commun 61:942, 1974
20. Pace-Asciak C, Wolfe LS: Biochemistry 10:3657, 1971
21. Bundy GL: Tetrahedron Letters 24:1957, 1975