Advances and Technical Standards in Neurosurgery

Edited by

L. Symon, London (Editor-in-Chief)
J. Brihaye, Brussels
B. Guidetti, Rome
F. Loew, Homburg/Saar
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Vol. 12

Springer-Verlag Wien New York

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Volume 12

Springer-Verlag
Wien New York 1985

With 49 partly colored Figures

Printed in Austria

Library of Congress Catalog Card Number 74-10499

ISSN 0095-4829
ISBN 3-211-81877-4 Springer-Verlag Wien—New York
ISBN 0-387-81877-4 Springer-Verlag New York—Wien

Sponsored by the
European Association of Neurosurgical Societies

Preface

As an addition to the European postgraduate training system for young neurosurgeons we began to publish in 1974 this series devoted to Advances and Technical Standards in Neurosurgery which was later sponsored by the European Association of Neurosurgical Societies.

The fact that the English language is well on the way to becoming the international medium at European scientific conferences is a great asset in terms of mutual understanding. Therefore we have decided to publish all contributions in English, regardless of the native language of the authors.

All contributions are submitted to the entire editorial board before publication of any volume.

Our series is not intended to compete with the publications of original scientific papers in other neurosurgical journals. Our intention is, rather, to present fields of neurosurgery and related areas in which important recent advances have been made. The contributions are written by specialists in the given fields and constitute the first part of each volume.

In the second part of each volume, we publish detailed descriptions of standard operative procedures, furnished by experienced clinicians; in these articles the authors describe the techniques they employ and explain the advantages, difficulties and risks involved in the various procedures. This part is intended primarily to assist young neurosurgeons in their post-graduate training. However, we are convinced that it will also be useful to experienced, fully trained neurosurgeons.

The descriptions of standard operative procedures are a novel feature of our series. We intend that this section should make available the findings of European neurosurgeons, published perhaps in less familiar languages, to neurosurgeons beyond the boundaries of the authors countries and of Europe. We will however from time to time bring to the notice of our European colleagues, operative procedures from colleagues in the United States and Japan, who have developed techniques which may now be regarded as standard. Our aim throughout is to promote contacts among neurosurgeons in Europe and throughout the world neurosurgical community in general.

We hope therefore that surgeons not only in Europe, but throughout the world will profit by this series of Advances and Technical Standards in Neurosurgery.

The Editors

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A. Advances

Prostaglandins, Thromboxane, Leukotrienes and the Cerebral Circulation in Health and Disease

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With 5 Figures

Contents

Arachidonic acid is ubiquitously distributed throughout the body and its derivatives form an extraordinary and bewildering array of compounds of widely differing properties. It is most unwise to generalize about how a given cell or tissue will utilize each pathway. This system responds to both physiological and pathological stimuli but the respective roles of the various products can be very difficult to unravel as will become all too apparent. The recent British Medical Bulletin (1983) provides an excellent overview of the subject. Von Euler (1936) created the term "prostaglandin" to christen the depressor, smooth muscle-stimulating acidic lipid that he and Goldblatt had demonstrated in human seminal plasma. Bergstrom began to determine the structure of this group of compounds in 1947 with publication in the early 1960s (for review, see Bergstrom *et al.* 1968). Following the isolation and description of the effects of the primary and relatively stable prostaglandins ($PGF_2\alpha$, PGE_1, PGE_2, PGD_2, etc.) came the discovery that prostaglandin synthesis was inhibited by the non-steroidal anti-inflammatory agents such as indomethacin and aspirin (Vane 1971). Certain discrepancies became apparent in the period 1970–1976 between the effects of prostaglandin synthesis inhibition and the effects of the known endogenous prostaglandins. Then, in rapid succession, came the description of the short-lived derivatives of arachidonic acid metabolism, including rabbit aorta-contracting substance (Palmer *et al.* 1973), the cyclic endoperoxides, PGG_2 and PGH_2, and thromboxane A_2 and its inactive metabolite thromboxane B_2 (Samuelsson *et al.* 1978, for review). Many tissues, particularly platelets, have the capacity to generate thromboxane A_2, which is very potent both at inducing platelet aggregation and in contracting smooth muscle. In 1976 came the description of the physiological antago-

nist to thromboxane A_2. Vane's group demonstrated that microsomes from arterial walls enzymatically transform PGG_2 and PGH_2 to an unstable product that relaxes arterial strips and prevents platelet aggregation-prostacyclin or PGI_2 (Moncada and Vane 1978, for review). Finally, the alternative lipoxygenase pathway for arachidonate metabolism has been explored recently and the whole family of so-called leukotrienes and lipoxins identified (Samuelsson and Hammerstrom 1980, Piper 1981, Serhan *et al.* 1984).

What is the current state of knowledge regarding the role of prostaglandins and other derivatives of arachidonic acid (eicosanoids) in the normal control of the cerebral circulation? Do these compounds have major roles in acute cerebrovascular disease—either in a damaging or in a protective capacity? Are the therapeutic regimes designed to alter the prostanoids in the brain based on a firm foundation, or are they meddlesome and likely to put patients at risk? This chapter updates our original reviews (Pickard 1981, Pickard and Walker 1984).

The Biochemistry of Arachidonic Acid Metabolism

Arachidonic acid is a twenty carbon polyunsaturated fatty acid with four double bonds (C20:4, eicosatetraenoic acid) found ubiquitously in phospholipids of cell membranes. It is obtained from the diet and also from dietary linoleic acid, an 18-C fatty acid which is converted by mammals to dihomo-γ-linolenic acid and arachidonic acid by chain elongation and desaturation. Arachidonic acid is oxidized enzymically to a large number of products which include the prostaglandins, thromboxanes, prostacyclin, the leukotrienes (some of which were known collectively as "SRSA"—slow reacting substance of anaphylaxis), and a variety of hydroperoxy- and hydroxy-derivatives (see Fig. 1) (Granstrom *et al.* 1982, Nelson *et al.* 1982, Moncada 1983). These are referred to collectively as "eicosanoids". Many of them have been demonstrated to have pharmacological properties in vivo and in vitro—these cover a very wide spectrum of activities. Although a number of other C20 polyunsaturated fatty acids (PUFAs) can be converted to prostaglandins (PGs), for example C20:5, C20:3, arachidonic acid is the commonest substrate, mainly because of its greater abundance.

The biosynthetic pathway from arachidonic acid to *prostaglandins* proceeds by incorporation of molecular oxygen to form an unstable endoperoxide intermediate PGG_2 (Figs. 1 and 2a). The hydroperoxy group (OOH) at C15 is then converted rapidly to a hydroxyl group (OH) forming PGH_2, another unstable endoperoxide. A single enzyme, cyclooxygenase, catalyses both these reactions. PGH_2 is susceptible to numerous enzymic

and chemical transformations. Reduction converts it to $PGF_2\alpha$. Two other products, PGE_2 and PGD_2, may be formed non-enzymically under non-reductive conditions, or enzymically. Glutathione is an essential co-factor for the PGE_2 isomerase. PGE_2, $PGF_2\alpha$, and PGD_2, differ structurally only in the substituent groups of their 5-membered ring. They are frequently

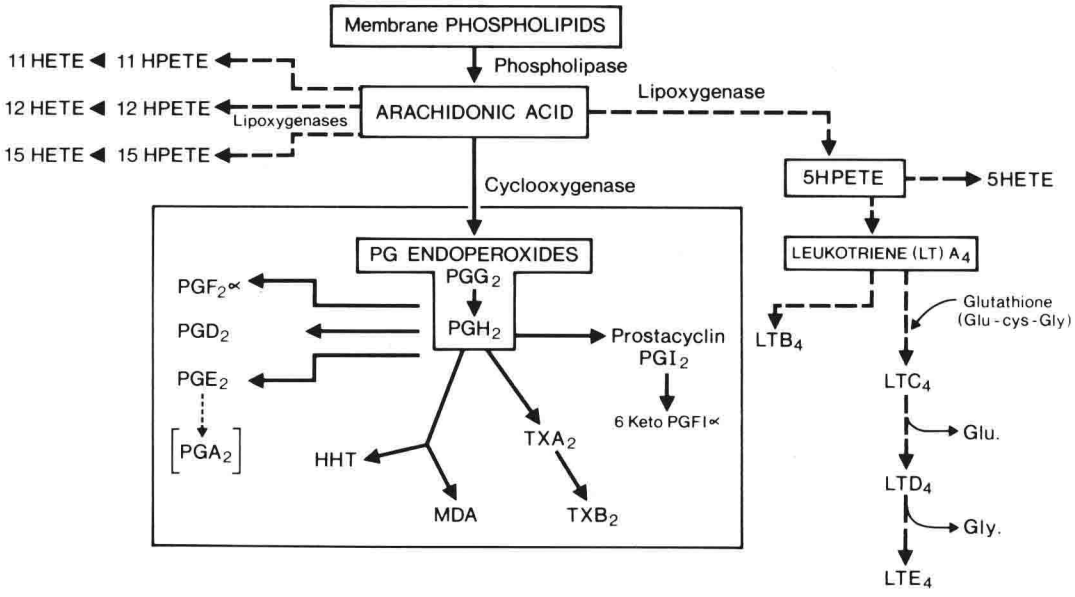

Fig. 1. Metabolism of arachidonic acid. ——→ cyclooxygenase pathway and products. — — — → lipoxygenase pathways and products. *PG* prostaglandin, *LT* leukotriene, *TX* thromboxane, *HPETE* hydroperoxy eicosatetraenoic acid, *HETE* hydroxy eicosatetraenoic acid, *HHT* 12 hydroxyheptadecatrienoic acid (17 carbon), *MDA* malondialdehyde (3 carbon)

referred to as the "Primary Prostaglandins". PGH_2 may be cleaved into a 17C fragment, 12 hydroxyheptadecatrienoic acid (HHT) and a 3C fragment, malondialdehyde (MDA). Alternatively PGH_2 may be converted to Thromboxane A_2 (TXA_2) or the bicyclic derivative prostacyclin (PGI_2; formerly PGX), by the enzymes Thromboxane synthetase and prostacyclin synthetase respectively. These are now known to be extremely important products of the pathway. Both are unstable. TXA_2 has a half life of 30 seconds, undergoing spontaneous conversion to a stable inactive metabolite, TXB_2. Prostacyclin has a half life of around 3 minutes in aqueous solution at PH 7.6, and is converted to a more stable hydrolysis compound 6ketoPGF1α (6oxoPGF1α). TXA_2 is a potent aggregator of platelets and

has a profound contractile effect on a variety of smooth muscles. Prostacyclin is the most potent natural inhibitor of platelet aggregation known, and at higher concentrations inhibits platelet adhesion. It is also a potent vasodilator of all vascular beds studied, including the cerebral

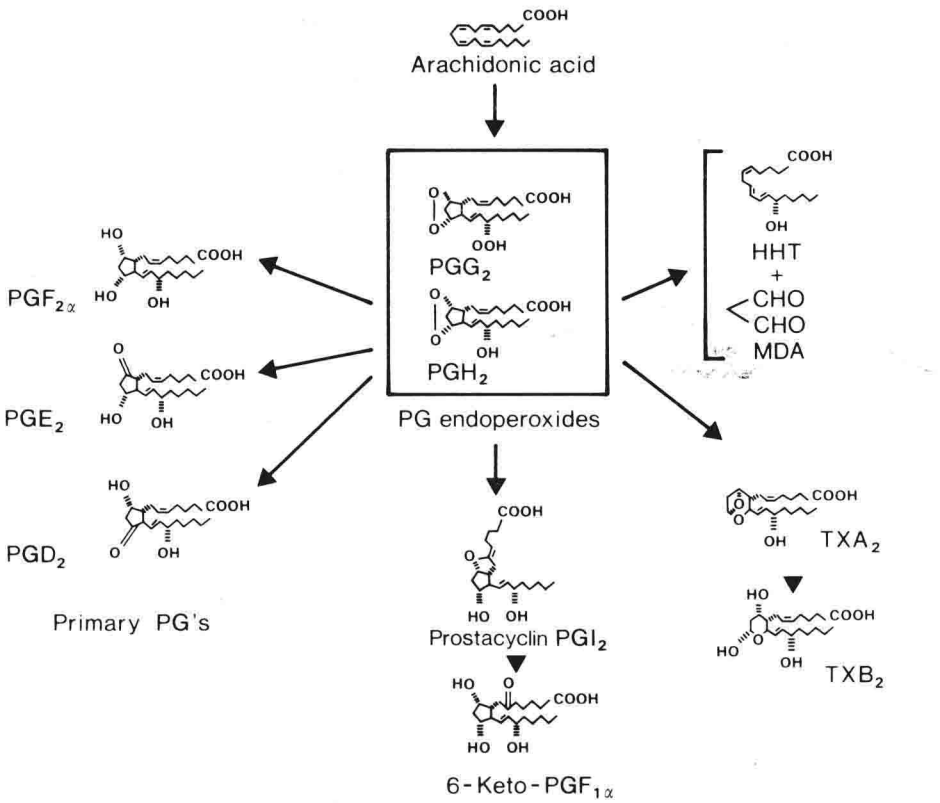

Fig. 2a. Some metabolites of arachidonic acid produced by the cyclooxygenase pathway (see Fig. 1 for key)

circulation (Moncada 1983). In the vascular system prostacyclin is produced mainly in the vessel walls, and TXA_2 in platelets. Although it has been demonstrated that arteries could utilize PG endoperoxides (PGG_2 and PGH_2) formed by platelets for prostacyclin synthesis (Bunting *et al.* 1983) this hypothesis has been challenged. Some believe that platelets do *not* normally provide endoperoxides for vascular prostacyclin production (Needleman *et al.* 1979, Granstrom *et al.* 1982).

If, instead of being acted upon by cyclooxygenase, arachidonic acid is oxidized by a group of enzymes known as *lipoxygenases*, a range of non-

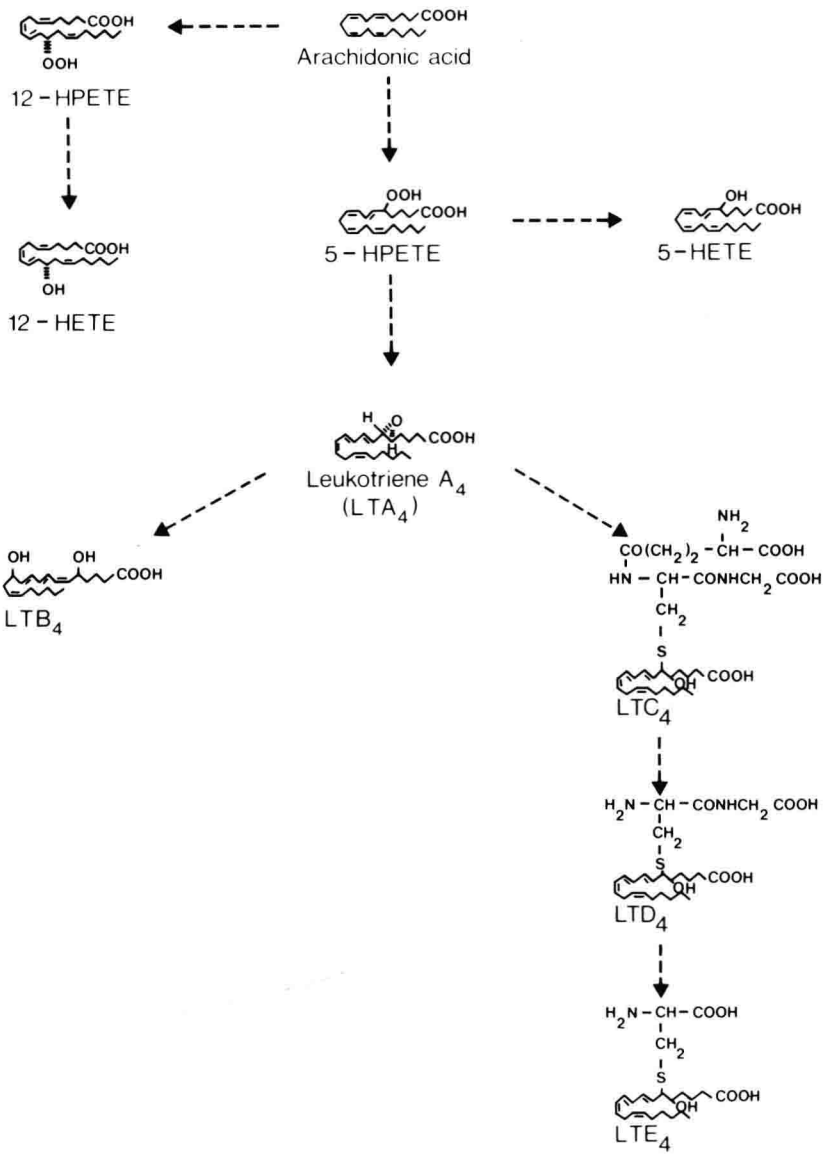

Fig. 2 b. Some metabolites of arachidonic acid produced by lipoxygenase pathways (see Fig. 1 for key)

cyclic hydroperoxy eicosatetraenoic acid derivatives (HPETEs) is formed (Figs. 1 and 2 b). These are named according to the site of the hydroperoxy (OOH) group within the molecule—viz 5-, 11-, 12-, or 15-HPETE. The hydroperoxy groups are readily reduced to hydroxyl (OH) groups, giving the corresponding hydroxy eicosatetraenoic acids (HETEs) viz 5-, 11-, 12-,