

Introduction to the biosynthesis and metabolism of prostaglandins

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THE prostaglandins are a family of lipid-soluble, unsaturated hydroxy acids containing twenty carbon (C) atoms and based on the prostanic acid skeleton. The C atoms in the molecule are numbered as shown in Fig. 1.

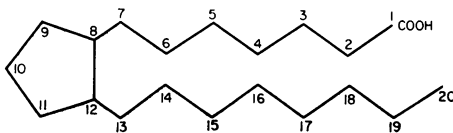


FIG. 1. Prostanic acid.

The prostaglandins are grouped according to the chemical groups on the pentane ring into types designated by the letters E, F, A, B, C and D. E-type prostaglandins have a ketone group at C9 and a hydroxyl group at C11. In D-type prostaglandins these groups are reversed, the ketone being at C11 and the hydroxyl at C9. F-type prostaglandins have hydroxyl groups at C9 and C11 and form isomers designated α and β , according to the plane of the hydroxyl groups. The A, B and C-type prostaglandins have a ketone group at C9 and 10-11, 11-12 and 8-12 double bonds respectively.

The prostaglandins are also grouped into mono-, bis- or tris-unsaturated classes according to the number of carbon-carbon double bonds in the side chain. The mono-unsaturated prostaglandins have only a 13-14 double bond, the bis-unsaturated have a 5-6 double bond in addition, and the tris-unsaturated have a 17-18 double bond also (Andersen, 1971). Prostaglandins E, F, A, B, C, D have a carboxyl group at C1 and a secondary alcohol group at C15.

Prostaglandins are not stored in tissues in a preformed state but are synthesized and released in response to a given stimulus (Piper and Vane, 1971). All types of mammalian tissue that have been examined are capable of synthesizing at least a small quantity of prostaglandins. Prostaglandins are synthesized from eicosatrienoic (dihomo- γ -linolenic), eicosatetraenoic (arachidonic) or eicosapentaenoic

acids. These compounds are incorporated in phospholipids and are converted to prostaglandins by the action of cyclo-oxygenase (Samuelsson, 1976). This enzyme, previously known as prostaglandin synthetase, is present in the microsomal fraction of cells and initially brings about cyclization and inclusion of molecular oxygen in the precursor. The action of cyclo-oxygenase (and therefore synthesis of prostaglandins) is inhibited by aspirin-like drugs (Vane, 1971; Lands *et al.*, 1974).

In the formation of bis-unsaturated compounds, for example when phospholipids have been hydrolysed by phospholipase A, arachidonic acid is acted on by cyclo-oxygenase or by lipoxygenase (which forms HETE but not prostaglandins). The cyclo-oxygenase initially stimulates formation of the cyclic-endoperoxides, prostaglandins G_2 and H_2 (Fig. 2). Prostaglandins G_2 and H_2 are then converted to either prostaglandins E_2 , D_2 , $F_{2\alpha}$ or thromboxane A_2 which is unstable and decays to thromboxane B_2 ; in some tissues, e.g. lung or platelets, the main products of arachidonic acid metabolism are thromboxanes rather than prostaglandins (Hamberg, Svensson and Samuelsson, 1976). Conversion of the endoperoxides to thromboxanes is enzymically controlled by thromboxane synthetase (Needleman *et al.*, 1976). As recently shown by Moncada *et al.* (1976), when prostaglandins G_2 or H_2 act on blood vessel walls prostacyclin (prostaglandin I_2) is formed enzymatically. The stable metabolite of prostacyclin is 6-oxo-prostaglandin $F_{1\alpha}$.

The possibility exists for some interconversion of prostaglandins, for example prostaglandin E_2 may be reduced to prostaglandin $F_{2\alpha}$ by the action of 9-oxo-reductase which is present in tissues of a number of species (Hensby, 1974). E-type prostaglandins are converted to A-type by acid or alkaline conditions (outside the range pH 5-8) and A-type rearranges to B in alkaline solution (Andersen, 1971). An isomerase present in plasma of some species converts prostaglandins A first to prostaglandin C and then to B (Jones, 1972).

Prostaglandins of the E and F series have a short

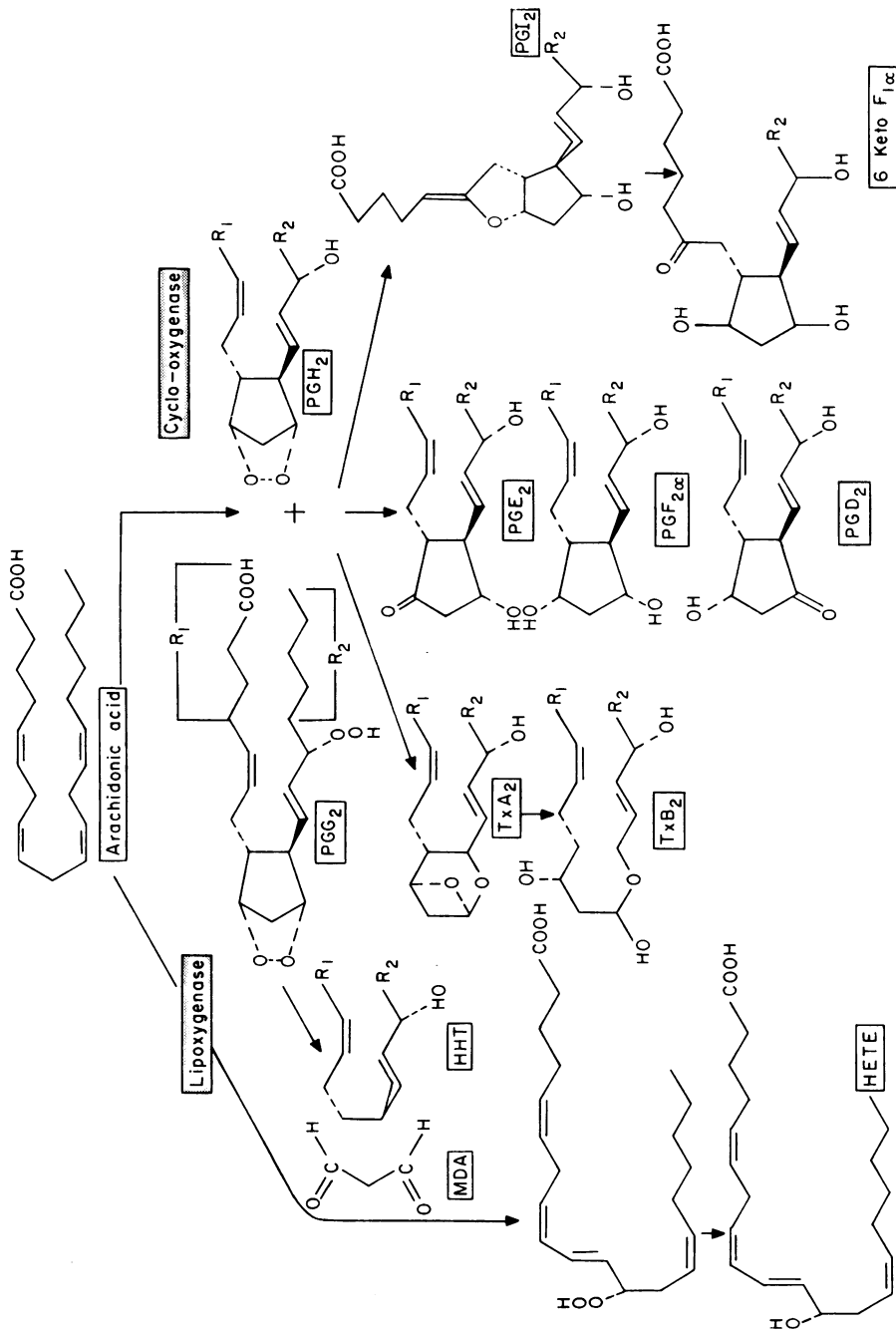


Fig. 2. Metabolism of arachidonic acid: synthesis of prostaglandins, thromboxanes and prostacyclin.

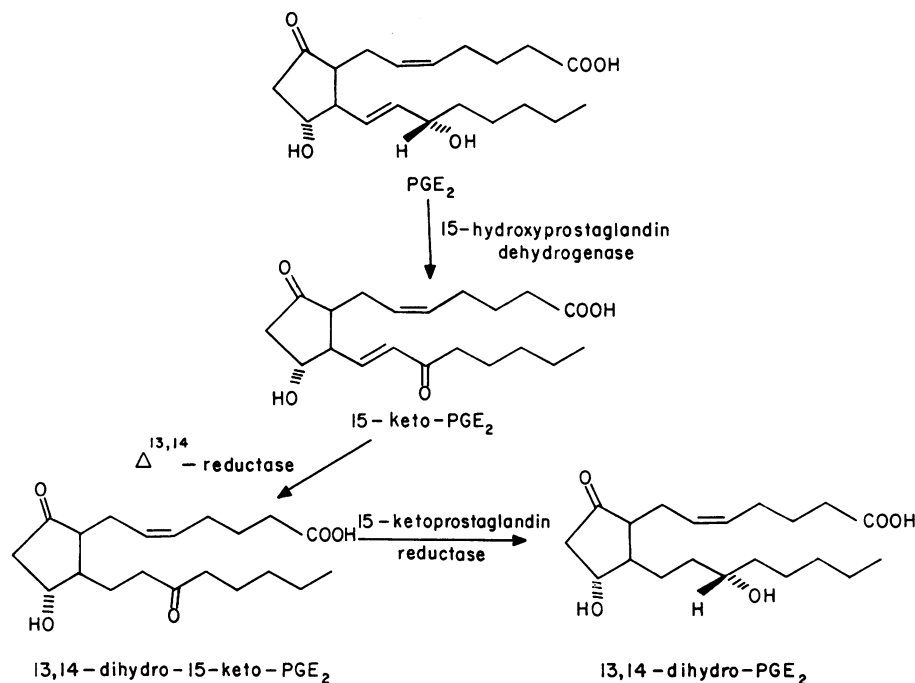


FIG. 3. Metabolism of E- and F-type prostaglandins.

half-life in the circulation and lose up to 95% of their biological activity on one passage through the pulmonary circulation and are further degraded on passage through other vascular beds (Ferreira and Vane, 1967). Initially the prostaglandins are taken up from the vascular space (Bito, 1975) and then metabolized by a series of enzymes to metabolites which usually have less biological activity than the prostaglandins (Crutchley and Piper, 1975). The enzymes are present in the soluble fraction of cells and are shown in Fig. 3. 15-OH prostaglandin dehydrogenase causes the oxidation of the secondary alcohol group at C15 which is the rate-limiting step in the breakdown of prostaglandins. A-type prostaglandins are not so rapidly metabolized by prostaglandin dehydrogenase and do not lose activity in the pulmonary circulation but in the hepatic portal circulation (Horton and Jones, 1969). A-type prostaglandins lose activity on conversion to prostaglandin B which is biologically inactive. The pulmonary metabolites of the prostaglandins are further broken down in the liver and kidney by β -oxidation to dinor- (eighteen C atoms) and tetranor- (sixteen C atoms) derivatives and finally undergo β -oxidation (Samuelsson *et al.*, 1971). The resulting metabolites are excreted in the urine and are biologically inactive.

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