The Prostaglandins and Their Influence on Lipid Metabolism

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Abstract

Isolation, characterization, occurrence, and physiological action of the prostaglandins are reviewed.

ABOUT 40 YEARS AGO Goldblatt (1,2) and von Euler (3) independently found that extracts of human seminal plasma stimulated a number of smooth muscle organs and caused a fall in blood pressure. The active material was named prostaglandin by von Euler, who showed that the activity followed the lipid soluble acidic fraction (4–7).

Isolation Structure

In 1957 Bergström and Sjövall isolated two crystalline compounds from sheep vesicular glands (8–10). One of these compounds, prostaglandin E_1 (PGE_1) showed both a strong vasopressor and smooth muscle stimulating activity whereas the other PGF_{1a} mainly showed the latter activity. Later two related compounds, PGE_2 and PGE_3 were isolated in pure form from the same source by Bergström et al. (11) and were found to have similar physiological properties.

Finally two additional prostaglandins, PGF_{2a} and PGF_{3a} have first been isolated from lung tissue (12,13).

The structure of PGE_1 was reported in 1962 by Bergström, Ryhage, Samuelsson and Sjövall (14,15). Further work has led to the elucidation of the complete structure of all the six prostaglandins isolated. Their structural interrelationship is shown in Figure 1 (16–20).

Occurrence

The wide distribution of the prostaglandins in different organs outside the male sexual organs is apparent from Table I.

The highest concns, however, have been found in sheep vesicular glands (9–11) and in seminal plasma (22,23). In the latter instance Bygdeman and Samuelsson (23) have developed a method for the quantitative determination of the prostaglandins in human seminal plasma of normal men. Their first average data were in μg per ml: PGE_1:20; E_2:20; E_3:4; F_{1a}:3; F_{2a}:3.

The concn in lung tissue was determined by isotope dilution and found to be about 0.5 μg of PGF_{2a} per gram of tissue (24).

Earlier reports of the occurrence of smooth muscle stimulating factors in human menstrual fluid, and in extracts of brain and iris have recently been reinvestigated and the activity has in all cases at least to a considerable extent been found to be caused by prostaglandins (cf. Table I).

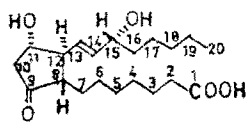
TABLE I

	E_1	E_2	E_3	F_{1a}	F_{2a}	F_{3a}	Reference
Seminal plasma							
Human	+	+	+	+	+		22,23
Sheep	+						21
Vesicular gland							
Sheep	+	+	+	+			8,9
Menstrual fluid		+			+		25
Lung							
Sheep		+			+		12,24
Cattle					+		
Guinea pig					+		26
Man					+		26
Monkey					+		26
Pig					+		12
Iris, sheep					+		27
Brain, cattle					+		28
Thymus, calf	+						29
Pancreas, cattle		+			+		30

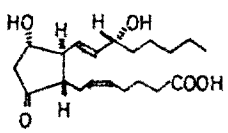
Biosynthesis

It was recently simultaneously reported by van Dorp et al. (31) and Bergström et al. (32) that tritium labeled arachidonic acid (all-*cis*-eicosa-5,8,11,14-tetraenoic acid) was converted into labeled PGE_2 in a high yield by homogenates of the vesicular gland of sheep.

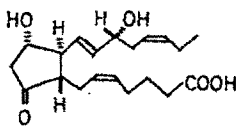
The expected conversion of homo-γ-linolenic acid into PGE_1 has subsequently been demonstrated experimentally with ^{14}C-labeled all-*cis*-eicosa-8,11,14-



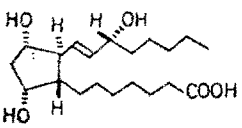
PGE_1 11α,15-DIHYDROXY-9-KETO-PROST-13-ENOIC ACID



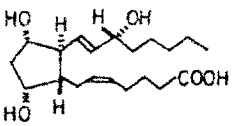
PGE_2 11α,15-DIHYDROXY-9-KETO-PROSTA-5,13-DIENOIC ACID



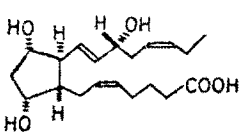
PGE_3 11α,15-DIHYDROXY-9-KETO-PROSTA-5,13,17-TRIENOIC ACID



PGF_{1a} 9α,11α,15-TRIHYDROXY-PROST-13-ENOIC ACID



PGF_{2a} 9α,11α,15-TRIHYDROXY-PROSTA-5,13-DIENOIC ACID



PGF_{3a} 9α,11α,15-TRIHYDROXY-PROSTA-5,13,17-TRIENOIC ACID

FIG. 1

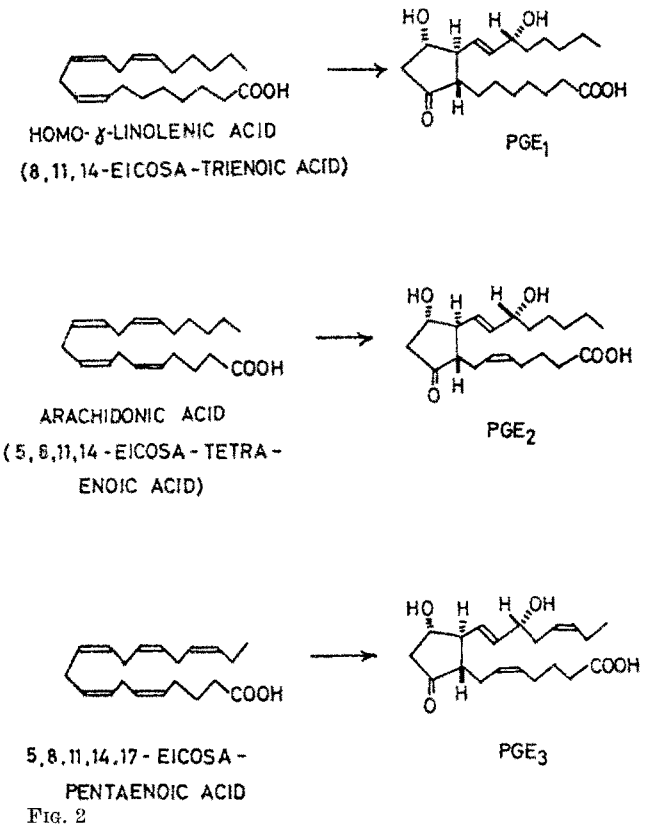


FIG. 2

trienoic acid (33,34). The formation of PGE_3 from all-*cis*-eicosa-5,8,11,14,17-pentaenoic acid has been demonstrated with unlabeled precursor by the net increase of PGE_3 in the homogenate (33) (cf. Figure 2).

The C_{22}-homologue of homo-γ-linolenic acid has been found to yield products with the expected physical properties (33) and the C_{19}-homologues of both homo-γ-linolenic acid and arachidonic acid have been found to yield nor-PGE_1 and nor-PGE_2 respectively (34). The corresponding C_{18}-acids, however, did not appear to be substrates for the enzyme system present in sheep vesicular glands.

These findings, that the physiologically highly active prostaglandins are directly formed from essential fatty acids, have provided a new approach to the study of the specific function of these fatty acids.

Biological Effects

The isolation of the prostaglandins has caused renewed interest in their physical and pharmacological properties and a number of in vitro and in vivo studies have been published. On a weight basis they are as active as epinephrine or norepinephrine in causing their specific pharmacodynamic action on the heart rate, blood pressure, etc., in animals and humans (35,36).

From a biochemical point of view the discovery of their effects on the metabolism of the free fatty acids is of special interest (37–42). Using rat epididymal fat pads in in vitro it was found by Steinberg et al. (37) that PGE_1 inhibited the basal release of glycerol as well as that stimulated by epinephrine, norepinephrine, glucagon, etc. In anaesthetized dogs, the marked increase in plasma-free fatty acids caused by continous infusion of norepinephrine (0.2 μg/kg/min) was blocked by simultaneous intraarterial injection of similar amts of PGE_1, PGE_2 or PGE_3, whereas the F-compounds are at least 10 times less active.

Prostaglandin E_1 has been found to counteract the permeability response of the toad bladder to vasopressin (43) and the E-compounds have pronounced effects on the central nervous system when injected intraventricularly (44,46).

Numerous studies of their action on organs containing smooth muscles, especially on the uterus and the tubes, have been published. References to these and other studies can be found in a number of recent review articles (45–49).

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