I N T R O D U C T I O N

I- HISTORICAL REVIEW

The history of Prostaglandins (PGs) goes back to 1930 when two American Gynaecologists Kruzrok and Lieb observed that strips of human uterus relax or contract when exposed to human semen.

A few years later, Goldbatt in England and Euler in Sweden independently reported smooth muscle contracting and vasodepressor activity in seminal fluid and accessory reproductive gland.(Goldblatt, 1935; Euler, 1936).

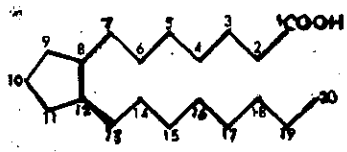
The term prostaglandin was coined in 1935 by Von Euler in the belief that the newly discovered biologically active substances originated from the prostate gland.

More than twenty years were to pass before technical advances allowed the demonstration that PGs were in fact a family of compounds of unique structure and permitted the isolation in crystalline form of two prostaglandins PGE_1 and $PGF_{2\alpha}$, and led to the elucidation of their structure.

In 1964 Bergstrom and Co workers and Van drops and associates independently achieved the biosynthesis of PGE_2 from arachidonic acid using homogenates of sheep seminal vesicles. Soon, more PGs were characterized and like the others. Proved to be 20 carbon

II- CHEMICAL STRUCTURE AND NOMENCLATURE"

PGs are a group of structurally related unsaturated fatty acid derivatives originating structurally from a hypothetical parent compound, prostanoic acid the structure of which is



Prostanoic Acid.

PGs are derived from 20-carbon essential fatty acids that contain three, form or five double bonds 8, 11, 14. eicosatrienoic acid (dihomogamma Linoleic A). 5, 8, 11, 14 eicosatetraenoic acid (Arachidonic acid), 5, 8, 11, 14, 17 eicosapentaenoic acid. They fall into several main classes, designated by letters and distinguished by substituents on the cyclopentane ring . These structures are. (Fig. I).

The main classes are further subdivided in accord with the number of double bonds in the side chains (Horton et al., 1978). This is indicated by subscript 1,2 or 3 and reflect the fatty acid precursor. Thus PGs derived from 8, 11, 14 eicosatrienoic acid carry the subscript I, those derived from arachidonic acid carry the subscript 2

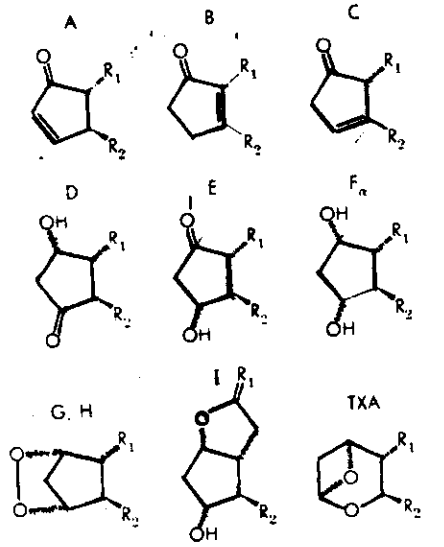


Figure 1-1. *Ring structures of the six "primary" prostaglandins* (A-F), *the cyclic endoperoxides* (G, H), *prostacyclin* (I), *and thromboxane A* (TXA).

In the stereochemical convention followed, the groups indicated by ▬ lie behind the plane of the cyclopentane ring, while those indicated by ◄ lie in front of it.

and those derived from 5, 8, 11, 14,17 eicosapentanoic acid carry the subscript 3.

The subscript Latin letter ∝ or B which is added e.g $PGF_{2\alpha}$, designates the configuration of C_9 hydroxyl group whether on the same side of the carboxyl group (∝) or on the opposite side (B). Most naturally occurring PGs have ∝ configuration except PGF which can also exist in the β configuration. PGs posses optical activity and the naturally occurring ones are Laevo rotatory (Bowman and Rand, 1980).

All PGs have a 15-hydroxy substituent and a trans double bond at the C_{13}-C_{14} position.

Both E, F series have a hydroxyl group at C_{11}.

The E series posses a ketone group at C_9 the F series has a second hydroxyl group at C_9, the A,B PGs may be regarded as dehydration products of the E series .

The endoperoxides G_2 and H_2 (PGG_2, PGH_2) have two oxygen atoms linking the C_9 and C_{11} position of the pentane ring. PGH_2 has side chain similar to that of classical PG, while PGG_2 has an extra oxygen atom between C_{15} and its (oH) group.

Thromboxane A_2 have an oxygen atom inserted into pentane ring.

Prostacyclin has an oxygen bridge liking C_9 of the pentane ring with C_6 of the side chain.

The six PGs of the E and F series $E_{1,2,3}$ and $F_{1,2,3}$ are often referred to as primary PGs, because non is a precursor of the other.

III- BIOSYNTHESIS

Synthesis of the primary PGs is accomplished in a stepwise manner by a ubiquitous complex of microsomal enzymes, the important of which is the cyclooxygenase enzyme (PG synthetase).

All mammalian tissue cells (except mature RBCs) have PG synthetase enzyme, which enables them to form PGs e.g kidney, lung, brain, spleen, uterus, heart, blood vessels, platelets and skeletal muscles (Pong and Levine, 1977, McGift, 1981).

Arachidonic acid which is the more abundant precursor is either derived from dietary linoleic acid or is ingested as a constituent of meal, is found as a component of the phospholipid, by estrification, or in an ester linkage in other complex lipids. It is released from membrane phospholipids by the action of the enzyme phospholipase A_2, the activation of this enzyme occurs in response to widely divergent physical, chemical, hormonal and neurohormonal influences. After arachidonic acid is liberated from its tissue stores, its conversion into PGs, thromboxanes or prostacyclin occurs through many steps in which tissue specific enzymes will direct the cascade towards the formation of PGs characteristic

for this particular tissue e.g formation of thromboxane A_2 TXA_2 in platelets (Hamberg et al.,1975) and prostacyclin. PGI_2 in the vascular wall (Moncada et al., 1976).

The steps involved in the biosynthesis of PGs are illustrated in Fig. (2), Briefly, PGG_2 is formed first, then it is spontaneously transformed into PGH_2 which is transformed enzymatically into PGE_2 mainly and PGD_2. $PGF_{2\alpha}$ may be formed directly from PGH_2, but mainly from PGE_2 under enzymatic action.

Again the final derivatives that are formed vary with the type of tissue, nature of substrate, the physiologic state of the animal, and the presence of injury or disease (McGift, 1981). e.g., PGI_2 is formed in vessel walls, while TXA_2 is formed in platelets.excess TXA_2 is formed in the presence of hyperlipedaemia (Stuart et al., 1980).

PGI_2 and TXA_2 are synthesized directly from PGG_2 each under the effect of its specific synthetase both are unstable compounds and rapidly disintegrate into the more stable metabolites 6-keto $PGF_{1\alpha}$ and TXB_2, respectively (Lands, 1979). 6-keto $PGF_{1\alpha}$ may still retain biological activities compatible to PGI_2 (Wong et al., 1981).

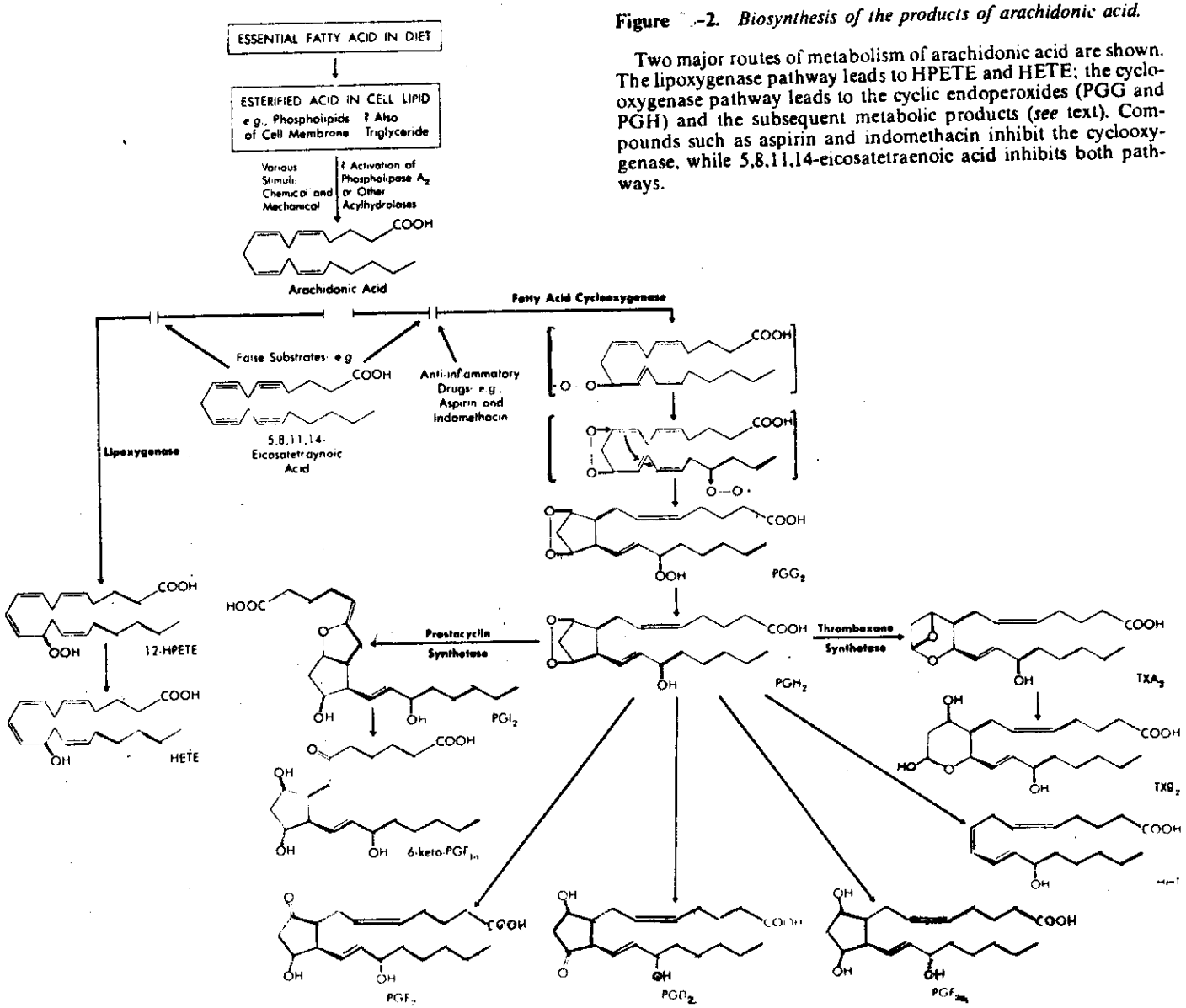


Figure 1-2. *Biosynthesis of the products of arachidonic acid.*

Two major routes of metabolism of arachidonic acid are shown. The lipoxygenase pathway leads to HPETE and HETE; the cyclooxygenase pathway leads to the cyclic endoperoxides (PGG and PGH) and the subsequent metabolic products (*see* text). Compounds such as aspirin and indomethacin inhibit the cyclooxygenase, while 5,8,11,14-eicosatetraenoic acid inhibits both pathways.

All the enzymatic steps involved in PGs biosynthesis are mediated via the PG. Synthetase, which is a multiple enzyme complex that include cyclo-oxygenases , reductases and isomerases, or it might be a one enzyme endowed with multiple sites (Pong and Levine , 1977) there is another way for metabolism of the fatty acids precursors by the enzyme lipoxygenase that catalyses also their oxidation. This enzyme system is found only in lung, platelets and white blood cells, by this enzyme system arachidonic acid is transformed into a hydroxyperoxide derivative HPETE and/or hydroxy derivative HETE, both can exert eosinophil chemotactic function (Tesch and kong, 1980). Samuelsson et al. (1980) named these products leukotrienes and demonstrated this new system to form the active part of the S.R.S.A.(slowly reacting substances of anaphylaxis). Lipooxygenase, unlike cyclo-oxygenase is not inhibited by compounds like aspirin and other non steroidal anti-inflammatory drugs. (NSAIDs).

When the cyclooxygenase enzyme is inhibited the metabolism of the released fatty acids will be directed towards the lipo oxygenase pathway (McGiff, 1981).

IV- CATABOLISM

Since PGs are locally acting hormones which are synthesized by all body cells, there must be a potent degradation system available for every cell and which efficiently protect the body against these biologically potent, even in minute doses, compounds. Efficient mechanisms exist for the catabolism and inactivation of most PGs, such activity is well illustrated by the observation that 95% of infused PGF_2 is inactivated during are passage through the pulmonary circulation (Ferreira and Vane, 1967).

The enzymatic catabolic reactions are of two types·an intial relatively rapid step catalysed by PG specific enzyme where in PGs lose most of their biological activity, and a second, relatively slow step in which these metabolites are oxidized by enzymes possibly identical to these responsible for β and W oxidation of most fatty acids·Degradation of PGE_2 as an example is summarized in Fig. (3). The initial step is the oxidation of the 15-oH group to the corresponding ketone group by PG-15-oH dehydrogenase (PGDH) (Hamberg and Samuelsson, 1971). The 15-keto compound is then reduced to the 13-14 dihydroderivative, a reaction catalized by PG Δ^{13}

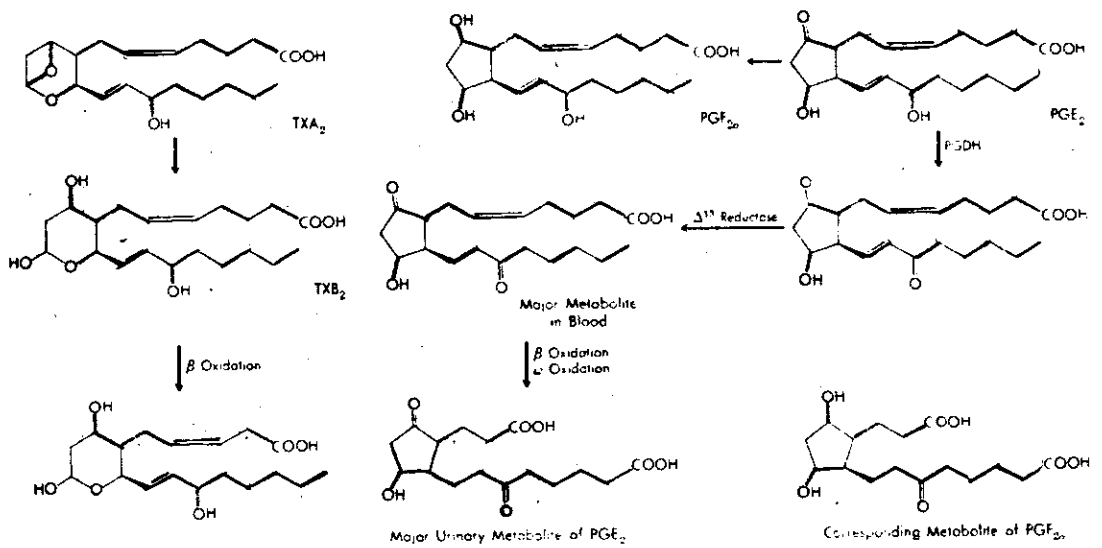


Figure 3. *Metabolism of PGE_2, $PGF_{2\alpha}$, and thromboxane A_2 (TXA_2).*

reductase (Anggard et al., 1971). While these first 2 reactions occur very rapidly, subsequent steps are slower, these consists of β and W oxidation of the side chains of PGs that provide the shorter mono and dicarboxylic acid which are the predominent PG metabolites in urine (Pong and Levine, 1977; Lands, 1979) .

Both PGI_2 and TXA_2 are unstable compounds, hence they are non enzymatically transformed into their metabolites 6 keto $PGF_1\alpha$ and TXB_2 (Land, 1979) .

The metabolism of TXA_2, a minor fraction is excreted unchanged after IV infusion and about 30% is excreted as the product of single B oxidation-dinor TXB_2 (Kindahl, 1977, Roberts et al., 1977).

The metabolism of PGI_2, as the majority of the metabolite , have a keto group at C_{15} suggests that a substantial fraction of the compound is metabolised by 15-oH PG dehydrogenase (Sun and Taylor, 1978).

V- CELLULAR MECHANISM OF PGs ACTION

Study of the cellular mechanisms mediating the effect of PGs on their receptors (response to receptor activation), like study of the fast-acting hormones, has focused primarily on the cyclic nucleotides and calcium. Both human platelets and RBCs constitute rather good models suitable for such a study, since they can be harvested in a relatively pure form. Platelets can synthesize their own PGs while the RBCs can only metabolize them. RBCs are sensitive to lowest concentration of PGs reported for any cell (Harris et al., 1979; Herrobin, 1978; Hittelman and Butcher, 1973).

a) Prostaglandin Receptors :

A number of distinct sites of PG action, which can be activated by very low concentrations of PGs have been identified because of their apparent high affinity and specificity for PGs. Such receptors have been evidenced in many tissue cells e.g PG receptors on adipocytes (Kuehl and Humes,1972), leucocytes , (Weinstein et al. , 1973), Corpus luteum (Rao et al., 1977), platelets (Siegl et al., 1978) and airways (Cepas et al., 1981). Although such receptors are specific for PGs, they apparently do bind various types of PGs despite those having different, even

opposing effects. A good illustration for this is shown in the airways where three classes of PG receptors are identified, an irritant class which leads to coughing, a relaxant class, and a constrictor class. All naturally occurring PGs can stimulate all the types of the 3 receptors but to varying degree (Copas et al., 1981). This observation can account for the seemingly inevitable irritation and cough encountered with PG inhalation, even when a bronchodilator PG is utilized and such dilator PGs can eventually cause bronchospasm.

b) Prostaglandins and the Cyclic Nucleotide System:

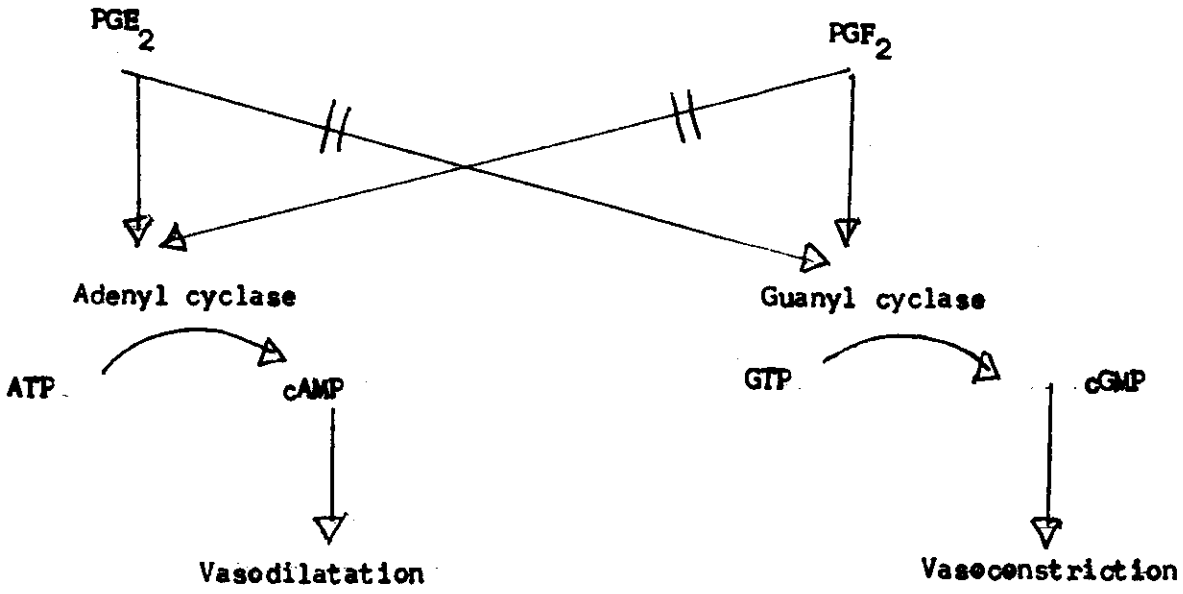
Sutherland and his followers (1968) have shown that the biological action of hormones and some drugs are mediated by a second messenger, cyclic AMP, formed in the cell membrane by the enzyme adenyl cyclase . Various hormones and drugs which increase the intracellular cyclic AMP concentrations also increase the release and concentration of PGs.

Many studies (White, 1974: Bourne, et al.,1974) indicate that a close relationship frequently exists between PG and cyclic AMP formation. PGE_1 or PGE_2 stimulates the activity of adenyl cyclase and increase cyclic AMP in many organs including the heart , lung, bone, leucocytes, RBCs, platelets and adrenals but PGE_1 inhibits the activity of adenyl cyclase and cyclic AMP in the

renal collecting tubules, stomach, adipose tissue and cerebellum.

Kuehl et al., (1973) postulated that PGs mediate the process between hormonal activation and cyclic AMP formation. Where in PGs would be second messengers of hormone action on the cell.

An alternative "Yin-Yang" concept has been offered by Goldberg et al. (1974) in which PGs are associated with the medulation of tissue cyclic AMP, cyclic GMP ratios, For instance, in a given tissue, PGE_1 or PGE_2 increases this ratio by increasing cyclic AMP and/or decreasing cyclic GMP whereas $PGF_{2\alpha}$ might decrease this ratio while exerting an opposite action .



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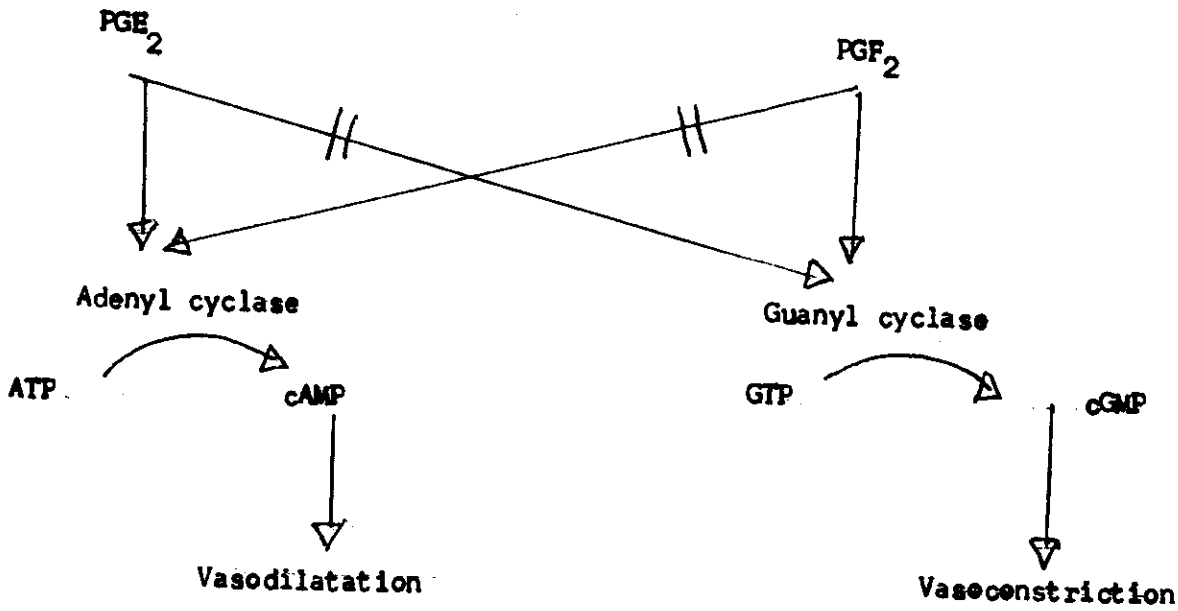

"Yin-Yang hypothesis for vascular actions of PGE_2, $PGF_{2\alpha}$"

c) Prostaglandin and Calcium :

Cellular action of PGs on the cell may be induced through their action on Ca ion.

Platelet aggregation induced by thromboxane A_2 is mediated through its ability to act as a calcium ionophore that translocates calcium from its storage sites (Harris et al., 1979). While PGE_2 which is also a platelet aggregator, acts by increasing calcium influx from the extracellular environment

On the other hand, prostacyclin(PGI)is a very potent antiplatelet aggregator, acting by inhibiting intracellular calcium release (Ally et al., 1978), or by increasing cyclic AMP levels (Siegl et al., 1978).

TXA_2, on the other hand, has no action on RBCs calcium (Harris et al., 1979). While other PGs affect RBCs calcium. PGE_1 can increase calcium levels inside the RBCs, resulting in activation of the membrane protein kinase, subsequently leading to increased deformability of the RBC, thus helping blood flow in the microcirculation because RBCs need to alter their shape in order to traverse capillaries. PGE_2 has opposite effect on calcium RBCs, and may induce sickling of susceptible RBCs at reduced O_2 tension (Harris et al., 1979). Also PGs affect norepinephrine release at the nerve endings through effect on Ca^{++} ion transport as shown in the figure.

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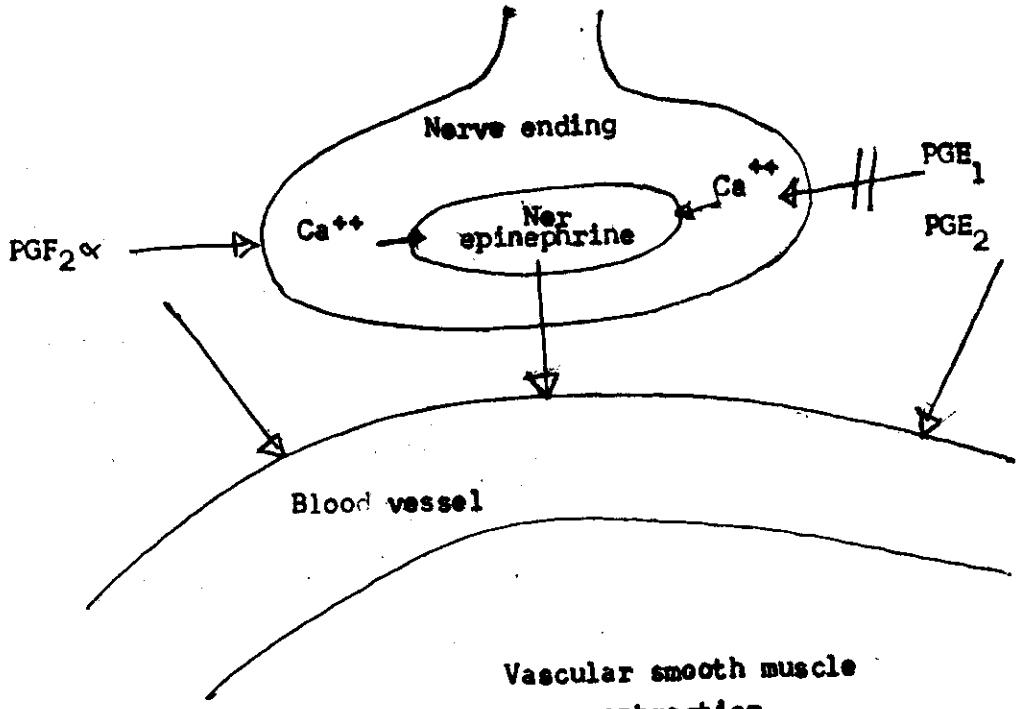

Hedqvist (1970) found that PGE_1 or PGE_2 infusion markedly inhibits norepinephrine release at the nerve endings through interference with intraneural Ca^{++} transport. $PGF_{2\alpha}$ appears to have the opposite action (Kadowitz et al., 1971).

d) Prostaglandins and Platelets :

(Endoperoxides, thromboxane)

All can affect the platelet function.

Thromboxane A_2 is regarded the primary mediator that induced platelet aggregation (Samuelsson and Hamberg, 1975); endoperoxides have the same effect on platelets but to a less extent. The half life of endoperoxides and TXA_2 in aqueous media are 5 minutes and 30 seconds

respectively (Hamberg and Samuelsson, 1975) but TXA_2 like activity may be still in plasma for 10 minutes whereas endoperoxides level seem to be negligable (Smith, 1976). The albumin of plasma may be responsible for stability of TXA_2 (Granstrom, 1977).

TXA_2 production depend on the presence of plasma. However in platelet-rish plasma aggregation induced by PGG_2 proceeds with little TXA_2 formation while in washed platelets TXA_2 is rapidly formed and distructed (Hamberg and Samuelsson, 1975). When the eggregation of platelets is inhibited by EDTA the TXA_2 formation continue for at least 3 minutes perhaps due to the slow release from metabolism of arachidonic acid or due to bound of endoperoxides to plasma proteins (Smith, 1976). In plasma PGH_2 may be converted to PGD_2 thus shortining life-time (Smith , 1976) .

e) Prostacyclin :

Is regarded the most potent in preventing aggregation of platelets which induced by different stimuli (Mon Cada et al., 1976). It is up to 30 times more active than both PGE_1 and PGD_2 (Moncada, 1976). PGI_2 also enhances disaggregation induced by PGG_2 and PGH_2 (Miller et al., 1977), the microsomes of vascular cells seem to produce PGI_2 from arachidonic acid and endoperoxides (Mon cada, 1976).

Hydroperoxy fatty acid is considered the potent inhibitor for PGI_2 synthetase at pH <7.

PGI_2 is rapidly converted to 6-keto $PGF_1\alpha$ which is relatively inactive compound. Recently it was found that 6-keto $PGF_1\alpha$ can also be converted to 6-keto PGE_1 which is active as PGE_1. The PGI_2 instability limits its value as an antithrombotic agent, on the other hand stable analogue of PGI_2 have been synthesized. (Corey, 1978).

VI- DISTRIBUTION, LEVELS AND RELEASE

Distribution and levels of concentration.

As previously mentioned human seminal plasma contains the highest PG concentrations in the body (Baum, et al., 1974). Some of the PGs are also found in various other tissues such as lung kidney, brain, spinal cord, pancreas , liver, thymus, iris, umbilical cord and placenta, PGs also occur in menstrual fluid, amniotic fluid and renal, splenic and adrenal venous blood. The major PG in semen is PGE_1 but in the majority of other tissues of various species including human tissue PGE_2 and $PGF_2\alpha$ predominate . (Karim et al., 1968).

Concentration of PGs in semen 250 ug/ml which is considered very high as the threshold concentration of PGs for biological activities are usually 1 ug/ml or less in different bio assay systems. In fact, the venous blood concentration of PGs after nerve or mechanical stimulation may increase to 200-300 ug/ml by novel biosynthesis and release of PGs in the tissue and the venous blood.

From birth through childhood, plasma PGE concentration is shown in the Figure (4) (Siegler, et al., 1977). The plasma PGE (mean $\pm$ SE) concentration in

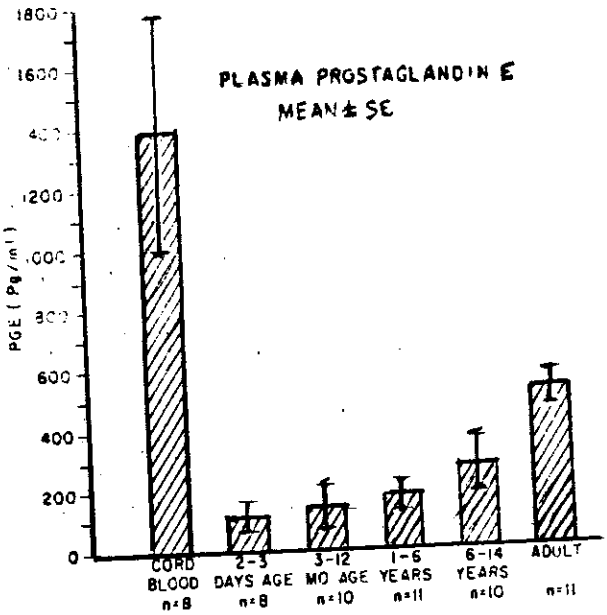

Fig. 4. Plasma PGE concentrations (mean ± SE) from birth through childhood.

the cord blood were 1,480 ± 390 P g/ml. this was significantly higher than normal adult level 530 ± 60 P g/ml. the PGE concentration in the same infants 48 to 72 hours later had fallen to 110±50 P g/ml. by 3 to 12 months of age PGE concentration had raisen to 140 ± 70 P gm/ml. PGE concentration continued to increase 181 ± 52 Pg/ml at 1 to 6 years of age and by 6 to 14 years of age they were 280±90 pg/ml. both values were significantly less respectively than those found in adults.

Craft and associates (1973) have found the concentration of $PGF_{2\alpha}$ to be significantly higher in the cord blood of human being than in the maternal circulation.

Challis and associates in (1976) have observed a substantial rise in circulating PGE during the last 24 hours of gestation but as placental transfer of $PGF_{2\alpha}$ and PGA have been demonstrated, much of the cord blood PGE is probably maternal in origin. The significant postpartum fall in PGE concentration noted by Challis and associates in lambs, and by Siegler et al.(1977) in human beings suggests that the newborn lung is quite capable of metabolising these substances, the low PG levels in infants and children could be secondary to decreased production, increased

catabolism or both. in 1974 Day and associates found the renal concentration of PGA and F to be substantially lower in a pair of human foetuses than in adult tissues. in addition, the seminal vesicles and the female reproductive tract, other significant sources of PG production, are poorly developed in the pre adolescent. The possibility that increased catabolism contributes to the low plasma levels must be considered, accordingly Pace Asciak (1973) has shown that PG catabolising enzyme activity is higher in the human newborn infant than in the mature rate.

Release :

PGs are not stored in tissues but rather biosynthesized and released on demand.

Many types of stimuli may trigger the biosynthesis and release of PGs. These stimuli are :-

- Physiological — nerve stimulation, hormones
- Physical — mechanical irritation
  trauma
  exposure to cold atmosphere
  x-ray irridiation, ultraviolet rays
- Circulatory and haematological
  -platelet aggregation.Sickle cell crisis
  -pulmonary troubles e.g embolism
  thrombosis, oedema

- Infection, parasitic infestation, toxaemia
- Immunological and allergic condition.

VII- Prostaglandins Inhibitors :

2 classes : A- Prostaglandin synthesis inhibitors

B- Prostaglandin antagonists.

A) PG Synthesis Inhibitor :

1) Inhibition of arachidonic acid release e.g corticosteroids.

2) Inhibition of the steps between arachidonic acid activation and endoperoxides formation, thus decreasing all classical PGs, thromboxane, prostacyclin e.g Aspirin, indomethacin.

3) Inhibitors acting distal to endoperoxides which may selectively inhibits some PGs but not others e.g imidazole inhibits thromboxane synthesis (Moncada et al., 1977). Copper ion and phenyl Butazone lower levels of PGE but not PGF in some studies, gold salts do the opposite action (Stone et al., 1975).

B) PG Antagonists :

These drugs act presumably by impending the accessibility of PGs to their sites of action blocking PG receptors or altering cellular events induced by PGs, e.gs.

- Certain compounds block the vasoactive properties of PGs such as quinine, quinidine, methylxanthines.

- Morphine blocks PG stimulation of adenylcyclase.
- Colchicine blocks the pro-inflammatory actions of PGs.
- Naproxene, block the action of PGs on intestinal or uterine smooth muscles (Stewart, 1981).

Prostaglandins and Inhibitors :

Prostaglandins and Salicylates :

Some years ago, aspirin was characterized as an antidefensive drug, inhibiting bodily reactions, such as fever, pain, inflammation that are thought to serve defensive function. At the same time it was agreed that aspirin acted by inhibiting an unidentified local humoral mechanism that mediated such reactions and that PGs are named among the humoral mediators possibly involved in that situations.

In 1971, Vane, proposed that the inhibition of PG synthesis that they had observed explains the anti-inflammatory, antipyretic and possibly some other in vivo effects of aspirin. Aspirin acetylates the amino-terminal serine group of the cyclo-oxygenase enzyme leading to irreversible inhibition of prostaglandin synthesis.

Acetyl salicylic acid is considerably more potent in platelets than in other tissue, as little as 20 mg/day

markedly inhibit thromboxane, PG synthesis and platelet aggregation (Burch et al., 1978). Since platelets can not synthesize new PG synthetase, antiaggregator effect of aspirin are long lasting (2 - 12 days), whereas in other tissue such as endothelial cells,the action is much shorter lived (1 - 2 days). Higher doses of salicylates may be required to inhibit prostacyclin than thromboxane or PG synthesis (Kimberly et al. , 1978).

2- PG and Indomethacin :

Rane and Samuelsson suggests that in vivo doses of less than 100 mg/day inhibits 80 % of total body PGE synthesis whereas doses of 150-200 mg/day achieve greater than 90% inhibition of PG synthesis (Rane et al., 1978). However in disease states, it is important to note that the usual therapeutic doses of 75 to 100 mg/day inhibit only from 15 to 60% of PG synthesis. The mechanism by which indomethacin inhibits PG synthesis remains unclear. Indomethacin inhibits cyclooxygenase by competitive reversible interaction at the substrate binding site to the enzyme or to a second regular site . At higher doses indomethacin may form a complex with iron in the metalloenzyme PG synthetase and then inactivate it (Peterson et al., 1979).

The action of indomethacin to inhibit cyclooxygenase

is time dependent and can be seen within minutes of direct application to the enzyme.
Indomethacin appears to inhibit total body PGE synthesis promptly with marked inhibition being apparent after 24 hours in vivo therapy (Samuelsson, 1973) , with a peak effect being visible after 48 hours.

3- Prostaglandins and Corticosteroids :

Glucocorticoids have recently been demonstrated to inhibit PG synthesis in at least some tissues. In rheumatoid synovial tissues, glucocorticoids inhibit PG synthesis by about 70% (Robinson et al., 1978) . On the other hand, corticosteroids do not inhibit phospholipase or PG synthetase in platelets although they inhibit thromboxane synthesis in leucocytes (Goldstein, 1977). In adipose tissue, unequally, corticosteroids may inhibit release rather than synthesis of PGs. The primary mechanism of action of corticosteroids appears to involve inhibition of the release of PG precursors (especially arachidonic acid) which will be acted upon by PG synthetase. Since this action requires new RNA and protein synthesis (Danon, 1978), it has been suggested that corticosteroids stimulate production of a protein which inhibit phospholipase A_2. Since the effects of corticosteroids require induction of new

protein synthesis, it is not surprising that their effects have a latent period of 1-8 hours for onset or offset in animal tissue in vitro (Danon et al. , 1978). In vivo treatment with glucocorticoids may require several days to achieve maximal inhibition of PG synthesis.

Since corticosteroids work at a different step in PG synthesis than many of other anti inflammatory agents,corticosteroids have the potential of being additive to indomethacin or aspirin. In fact corticosteroids have been reported to increase excretion of salicylates (Klinenberg, 1965) an effect which counter balance any benefit from additive mechanisms of inhibition of PG synthesis.

VIII- SOURCES OF SUPPLY

1) Direct Extraction from Tissues :

It has been observed that PGs can be extracted from a remarkably wide variety of animal tissues. this extraction involves a series of organic solvent extractions and partition to separate hydroxy fatty acids from other biologically active substances. Intial extraction with ethyl alcohol is usually followed after alcohol evaporation by partition of an aqueous acidified solution of the extract with an organic solvent such as ether or ethyl acetate. Group separation of E,F and A PGs is achieved by silicon gel or silicic acid chromatography (Daniels and Pike , 1968). Separation and identification of individual PGs within a group is effected by column chromatography or thin layer chromatography in several different solvent systems (Green and Samuelsson, 1964).
Direct extraction from mammalian tissue does not constitute a potential means of obtaining significant quantities owing to the very low concentration in which they occur.

2) Biosynthesis in Vitro :

This method is only able to provide natural PGs and is not suitable for preparation of PG analogues

PGE can be obtained by incubating vesicular gland homogenates (an enzyme source) with 20 straight chain carboxylic acid (Wallache, 1965). Moreover $PGF_{2}\alpha$ series can be obtained by using lung homogenates as enzyme source (Anggard and Samuelsson,1965).

3) Total Chemical Synthesis :

The advantage of total synthesis is that unlike biosynthesis, its potential scope is unlimited , it makes possible not only the large scale production of the natural PGs but a while range steroisomers and analogues some of which may be valuable in overcoming some of the short coming of the natural PGs in clinical practice such as their brief duration of action or side effects. Total synthesis of PGE_1 $F_1\alpha$, E_2 and $F_2\alpha$ have been recently reported , two main schemes have been developed by ~~the unjohn groups~~ of scientists (Axen et al., 1972) and by (Corey and his associates 1971) both of which are versatile to permit synthesis of all primary PGs (E_1, E_2, E_3, $F_1\alpha$ $F_2\alpha$ and $F_3\alpha$).

IX- Prostaglandin Assay :

There are three types of assays are in use each type of assay has its uses but no one is truely satisfactory for the investigation of the physiological and pathophysiological roles of the PGs. One of the main

problems which has limited the value of assays is that any disturbance of any cell leads to pour out of its PG content within seconds. This makes it extremely difficult when measuring the PG content of any body fluid in contact with cells. Another major problem is the great instability and rapid degradation of most PGs particularly TXA_2 and PGI_2 as a result many workers shifted to measure the metabolites of PG such as TXB_2 instead of TXA_2 and 6-keto $PGF_1\alpha$ instead of PGI_2 and 15-keto and 13-14 dihydro-15 keto metabolites instead of PGE_2 and $PGF_2\alpha$.

1) Biological Assay :

More sensitive type has 2 ways, first extraction and chromatographic separation of PGs using various smooth muscle preparations (Horton and Main et al., 1967). then 2nd directly measure the PG content of tissue fluids (blood or saline perfusates) by superfusing a series of tissue in a cascade done successively by Vane 1969. Difficulties will arise if more than one PG is present.

2) Radioimmunoassay :

Shaw and Ramwell (1969) predicted that antibodies could be generated against PGs with a protein molecule and that radioimmunoassay of PGs would then be possible.

This prediction was realized 1970 with the first report of radioimmunoassay of $PGF_2\alpha$ (Levine and Vane Vunakin, 1970). This method has the immense advantage of high sensitivity.high specificity and the ability to cope with large numbers of samples simultaneously. However it has some important limitations. First not all PGs and their metabolites are available for such tests, moreover compounds as yet unidentified, undoubtly exist in biological fluids that may cross react with the antiserum. A second limitation is the availability of reagent namely, specific antisera and radioactivity labelled PGs, these are now available for some of the major PGs and their metabolites, other PGs can not yet estimated by this method e.g PGD and 19 hydroxy PGE_2. Using radioimmunoassay, PGs concentrations have been measured in human plasma levels of PGE and F are normally 100-400 mg/ml whereas levels of PGA are in the range of 1 ng/ml (Bernard and Cherles et al., 1973).

3) Combined gas chromatography and mass spectrometry

This is the ultimate tool in the identification of PGs.it is as specific and sensitive method of PG assay capable of measuring PGs in the microgram range (Horton, 1972).