PROSTAGLANDINS IN CHRONIC RENAL DISEASES

THESIS

SUBMITTED IN PARTIAL FULFILMENT
FOR THE MASTER DEGREE IN
(GENERAL MEDICINE)

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CAIRO — EGYPT

1986

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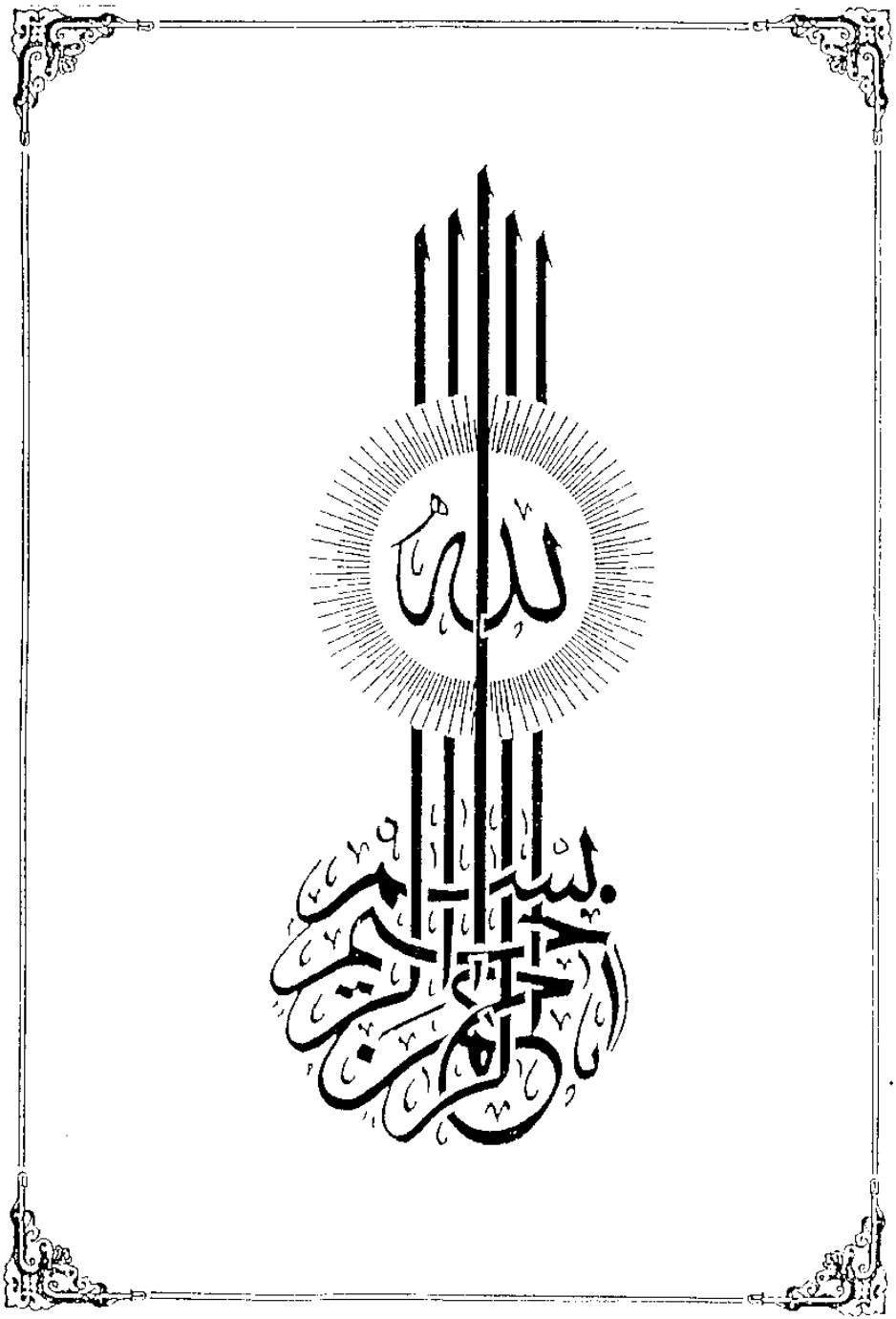

ABBREVIATIONS

PGs = Prostaglandins.

EFA = essential fatty acid.

LA = Linoleic acid.

GLA = gamma - Linoleic acid.

A.A = Arachidonic acid.

Tx = Thromboxane.

CAMP = cyclic adenosine monophosphate.

CGMP = cyclic guanosine monophosphate.

R.I.A = Radioimmunoassay.

Ca = Calcium.

NAD = nicotinamide adenine dinucleotide.

Na = Sodium.

RBC = Red blood cell.

B.P = blood pressure.

ACKNOWLEDGEMENT

I would like to express my deepest gratitude and most sincere thanks to Dr. Hussein El-Damasy, Prof. of General Medicine in Endocrine Unit, who gave me the broad outline of such subject, for close supervision and great co-operation throughout the whole course of the study.

I wish to express my deepest appreciation and thanks to Dr. Saad Abd El-Hagid, Assist. Prof. of General Medicine who offered me the generous support and many useful criticisms and suggestions throughout this study.

I wish to express my thanks to Dr. Sohair Gamal El-Din, Assist. Prof. of General Medicine in Endocrine Unit for her precious guidance and continued supervision during this work.

I owe my thanks to all the biochemists of the endocrine lab. for performing the hormonal assay with me.

Last and not least, I am grateful to all patients who have shared in this study by their own blood.

INTRODUCTION AND AIM OF THE WORK

The discovery of prostaglandins was first done by Von Euler (1935), who demonstrated the presence of such biologically active substance in human seminal fluid.

Prostaglandins are derivatives of polyunsaturated fatty acids. They are widely distributed in animal and human tissues.

There are eight major series known as parent prostaglandins A,B,C,D,E,F,G and H. Within each series there are members differing in the degree of unsaturation (Nelson 1974).

PG synthetase is complex enzyme system required for biosynthesis and have been demonstrated in most mammalian tissues. (Christ and Vane Dorp, 1972).

PGs are not stored in the cells as such but are synthesized when they are needed (Pace - Asciak and Wolf, 1968). Aspirin and other non steroidal anti-inflammatory drugs inhibit PG biosynthesis (Flower, 1974), while anti-inflammatory steroids inhibit their release. (Lewis and Piper, 1975). They are biologically active in minute amounts and have short half lives as they are rapidly metabolized especially by the lung (Samuelsson et al, 1971). The pharmacological action of natural PGs are numerous. Some stimulate the pregnant myometrium (Karim, 1972), other inhibit gastric secretion (Horton et al., 1968), dilate the bronchioles, reduce arterial blood pressure,

increase venous return to the heart, increase blood flow to vital organs and control the Functions of various endocrine organs. PGs are synthesized and released from renal cortex and medulla can affect renal blood flow, renin release, salt and water balance as well as vascular tone.

The aim of this present study is to clear out the correlation between changes in PG level in the plasma and renal dysfunction in patients with chronic renal diseases.

PROSTAGLANDINS

Nomenclature:

Prostaglandins are derivatives of a hypothetical substance, Prostanoic acid which is a 20 - Carbon atom, unsaturated hydroxy fatty acid with a cyclopentan ring at C_8 - C_{12} attached to it two straight side chains, one of them at its terminal end. The five membered ring is substituted in various ways; accordingly PGs are divided into A,B,C,D,E,F,G,H, and R Families that differ from each other in the functionality of this ring. Prostaglandins of G,H, and R Families have the same substitution of five membered ring, however PGH and PGR are identical while PGG differ by the attachment of 15-L hydroxy group. Each family is further subdivided and identified by a numeric subscript according to the number of double bonds in the side chain. (Nelson 1974).

The most common types of PGs are A,B,C,D,E and F with their three series, 1 series, 2 series and 3 series. Although all of them were isolated and studied, some of them are doubted to exist in nature and are suggested to be artefacts of the extraction procedures, hence PGs of A,B,C,D,E and F are referred to as parent PGs, although the name was earlier attributed to the earliest isolated ones (Mc Giff, 1981).

Chemical Structure:-

All natural PGs posses an oxygen atom at C_9 (alcohol or ketone), for example PGE contains aketone group at the same position. They also contain ahydroxyl group at C_{15} position and a double bond linking C_{13} with C_{14} (Bergstrom et al., 1962).

The subscript number is added after the capital letter to indicate the number of double bonds in the straight side chains, PGE_2 has two double bonds and PGE_3 has three double bonds. This subscript number also indicates the fatty acid precursor from which the PG originates. The "1" series originates from linolenic acid while the "2" series is originating from arachidonic acid. This "2" series is the commonest PGs naturally existing due to the abundance of arachidonic acid, while the "1" series is less common and the "3" series is very rare in nature and may not even exist. The subscript latin letter (α or β) is added to designate the configuration of C_9- hydroxyl group, whether on the same side of the carboxyl group (α) or on the opposite side (β) for example $F_{2\alpha}$ and PG F_2B.

Most of the naturally occuring PGs have α - configuration except PGF which can exist also in the β form. So α and β subscript should be added when PGF is concerned. Thus

PGs posses optical activity and the naturally occuring ones are laevo-rotatory. (Bowman and Rand, 1980; Zurier, 1980).

Isomerism:-

All PGs are capable of having sterioisomeric forms but asingle isomer of each type has been isolated from mammalian sources except 9-beta-OH metabolite found in guinea pig (Bergstrom et al 1962).

Instability:-

The β ketal radicle of PGE_1 is stable only in neutral PH range. At PH below (5) dehydration occurs and PGE changes to PGA which in turn is rearranged to form PGB under alkaline condition (Miyano et al., 1971).

Biosynthesis:-

All mammalian tissue cells can synthesize PGs except mature red blood cells. e.g:- kidneys, lungs, brain, spleen uterus, heart, blood vessels, white blood cells, platelets, and skeletal muscles, as all of these tissues contains prostaglandin synthetase enzyme. (Pong and Levine, 1977; Lands, 1979; MCGiff, 1981).

1) Substrate Availability:-

PGs are derived from essential fatty acids (EFAs) of linoleic acid (LA) family. There is agood evidence that the main function of essential fatty acids is to give rise to PGs and there is acorrelation between the activity of essential fatty acid and its liability to act as a precursor of PGs (Beerthuis et al., 1968). Linoleic acid is an 18 C acid with 2 double bonds. It is desaturated to give gamma - Linoleic acid (GLA) which is in turn elongated to give dihomo-gamma linolenic acid (DGLA).This latter is the precursor of "1" series PGs and when desaturated it gives arachidonic acid (AA) which is the precursor of the "2" series, however arachidonic acid is present in diet as such in daily intake but at low concentration. Arachidonic acid is the most abundant precursor of PGs and most authors when discussing PGs synthesis refer to A.A directly. Arachidonic acid is not found free in the body under normal condition, but is found esterified on the inner side of cell membrane in the form of phospholipids.

2) Phospholipase A_2:-

Release of arachidonic acid from phospholipids is under the effect of phospholipase A_2 enzyme. (Kunze

and Vogt, 1971). Phospholipase A_2 may be aregulating factor (Vogt et al 1966) as perfusion of guinea pig lung or frog intestine with it leads to the appearance of a large amounts of PGs in the perfusate. This enzyme is rapidly activated in response to many stimuli (hormones, inflammation, mechanical and physical injuries). These stimuli have in common a distortion effect on the cell membrane with consequent release of calcium from its store sites or stimulating its entery inside the cells. This calcium in turn activates the phospholipase A_2 (Markelonis and Garbus, 1975; Pickett et al, 1977). Other lipase enzymes may be involved in releasing the substrate (F.A) from other complexes as triglycerides and cholesterol esters e.g triglyceride lipase, diglyceride lipase and hydrolases (McGiff, 1981). After release of arachidonic acid from its tissue stores, its conversion to PGs, thromboxanes (TxA_2) or prostacyclin (PGI_2) occurs through many steps in which tissue specific enzymes direct the cascade towards the formation of PGs characteristic for that tissue e.g (TxA_2) in platelets (Hamberg et al; 1975) and PGI_2 in the vascular wall (Moncada et al; 1976).

3) Prostaglandin synthetase: (cyclooxygenase; PG endoperoxide synthetase).

It is a multiple enzyme complex that include, cycooxygenase, reductases and isomerases or it might be one enz-

yme with multiple sites (Pong and Levine, 1977). It is located in the microsomal Fractions of all mammalian cells except mature red blood cells (Pong and Levine, 1977 Lands, 1979). It mediates the transformation of the substrate (EFA) into the unstable PG-cyclic endoperoxides (PGG_2 and PGH_2) PGG_2 is formed first, then it is spontaneously transformed into PGE_2 (mainly) and PGD_2. $PGF_{2\alpha}$ may be formed directly from PGH_2 but mainly from PGE_2 enzymatically. PGI_2 and PGA_2 are synthesized directly from PGG_2 each under the effect of its specific synthetase, however, both are unstable compounds and rapidly disintegrate into the more stable metabolites 6 Keto PG $F_{1\alpha}$ and TxB_2 respectively (Lands, 1979). 6 Keto $PGF_{1\alpha}$ may still retain biological activities. (Wong et al; 1981).

Inhibition of Biosynthesis and Releasc:-

Anti-inflammatory steroids can inhibit the release of PGs (Lewis and piper, 1975). They block the release but not the synthesis. It is more probable that they interfere with the release of PG precursor rather than PGs themselves.

Vane (1971) discovered that aspirin blocks PG biosythesis and this discovery led to the conclusion that this mode of action accounts for the therapeutic effects of this and related drugs (Flower, 1974).