EFFECTS OF INDOMETHACIN ON SERUM ALDOSTERONE AND CORRELATED ELECTROLYTES

Thesis
Submitted in Partial Fullfilment
for Master Degree in Medicine

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1987

بسم الله الرحمن الرحيم

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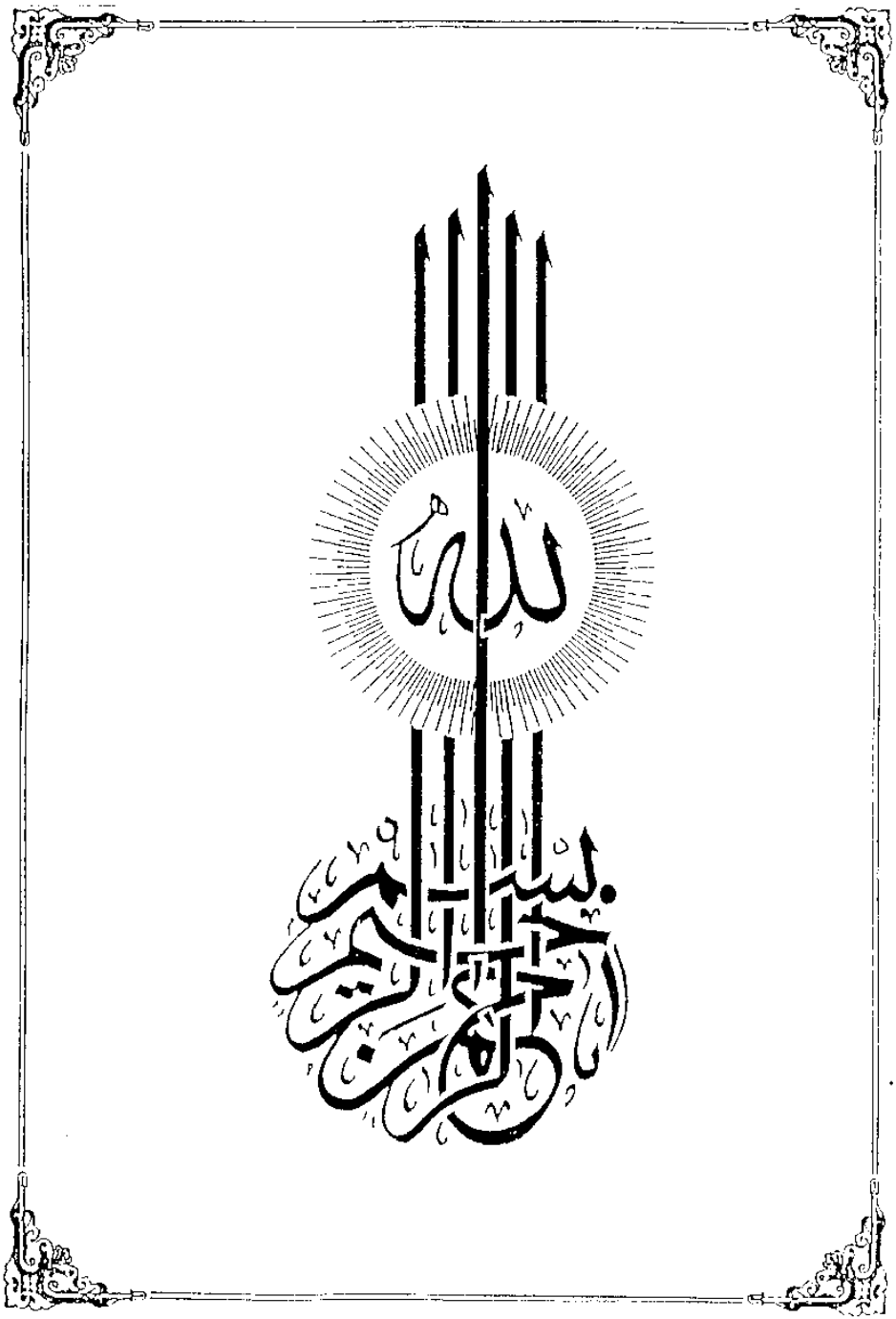

CONTENTS

REVIEW OF LITERATURE

ACKNOWLEDGEMENT

I would like to express my deep gratitude and appreciation to ***Dr. SAMIR SADEK,*** *Professor of Medicine, Faculty of Medicine, Ain Shams University, who devoted a great deal of his time and effort during conduction of this work, for his enthusiasm, encouragement as well as for his untiring support and help, inestimable assistance and valuable creative suggestions.*

I feel gratefully indebted to ***Dr. MOHAMED AMIN FIKRY,*** *Professor of Medicine, Faculty of Medicine, Ain Shams University, who by his extensive guidance, kind suggestions and considerable help contributed in a very real way toward the completion of this study.*

My sincere thanks to ***Dr. FADILA GADALLAH,*** *Lecturer of Medicine, Faculty of Medicine, Ain Shams University, for her unfailing interest, kind help and considerable co-operation.*

Deepest thanks to Major General ***Dr. AHMOS KAMEL GABRIAL,*** *the Head of Clinical Pathology Department, Air Forces Hospital, for his steady encouragement valuable help in placing Lab. facilities for the research work and his kind suggestions.*

My deepest thanks also extended to the staff members of Medicine and Rheumatology Departments, Air Forces Hospital, for their help and considerable co-operation.

PROSTAGLANDINS

The prostaglandins are unsaturated fatty acid compounds derived from 20-carbon essential fatty acids the most important of these precursors in human beings is arachidonic acid. Prostaglandins are uniquitous in their distribution throughout the body, and they function for the most parts as "local hormones". Their biological activity is exerted primarily at the site of their synthesis, since they have a short half-life in the circulation. Furthermore they are probably not stored but rather synthesized immediately before release a process initiated by liberation of arachidonic acid from the phospholipid pool of the cell membranes **(Samuelsson et al., 1978).**

Synthesis

Gerrard and Graff (1980) *stated that the initial step in synthesis of prostaglandin (and related compounds) involves cleavage of arachidonic acid from estrification sites in membrane phospholipids and to a lesser degree in triglycerides and cholesterol esters. One enzyme which is clearly important in some cells in this action is phospholipase* A_2*, which cleaves arachidonic acid from phosphatidyl choline, phosphatidyl linosital, phosphatidylserine, and phosphatidylethanolamine. They added that the free arachidonic acid must then reach the microsomes which is the major site of prostaglandins synthesis.*

In the microsomes a critical enzyme complex subserving 2 enzymatic function act upon arachidonic acid **(Sameulsson et al., 1978),** *the first cyclo-oxygenase adds molecular* 0_2 *to the fatty acid and cyclizes it to the cyclic endoperoxide PG.G2. PG.G2 is then acted on by the second function of the enzyme there by converting PG.G2 to PG. H2.* **Goetzl (1980)** *stated that PG.H2. can be converted by one of several other enzymes (isomerases and reductases) to one or more of the classic prostaglandins (PG.E2, PG. F2 a, PG.D2) or, via prostacyclin synthetase or thromboxane synthetase to prostacyclin (PG. I2) or thromboxane respectively. Arachidonic acid gives rise to prostaglandin of dienoic series (prostaglandin E2). Triene and pentaene analogues of arachidonic acid, which yield prostaglandin El and E3 respectively are not present in significant amount.*

Arachidonic acid

Lipooxygenase

1. *HETE*
   (12-hydroxy arachidonic acid)
2. *HPETE*
   (12 hydroperoxy arachidonic acid).

N.B.:

Little is known about the Pharmacological activity or further metabolism of HPETE, HETE.

Although HETE has a chemotactic action for polymorphnuclear and alveolar macrophages.

Cyclooxygenase

Prostaglandin G^2 *(PG* G^2*)*

$PG\ H_2$

Thromboxane A_2 *(unstable)*

Tx^bB_2 *(Stable)*

Isomerization enzymatically or non enzymatically

PGE_2 *or* PGF_2 *or* PGD_2

Prostocyclin (PGI_2)

(Moncada et al., 1980)

Pharmacological properties of prostaglandins:

I. *Gastrointestinal Effects:*

A) They affect smooth muscle throughout the gastrointestinal tract. Longitudinal muscles are contracted by P.G.E. & F circular muscle are relaxed by PGE and contracted by P.G.F.

About the effect of prostaglandins on oesophageal motility P.G.E_1 & PGE_2 relax the lower oesophageal sphincter while P.G.F. contract the lower oesophageal sphincter **(Rattan et al., 1972).** *Relaxation of the pyloric sphincter by prostaglandins was reported by* **Horton et al., (1968)** *as oral administration of P.G.E. is not associated with reflux of bile into the stomach.*

About the effect of prostaglandins on intestinal motility Horton and his co-Workers (1968) first reported the occurrence of augmented intestinal peristalsis with watery diarrhoea following oral adminstration of P.G.E_1. It induce contraction of longitudinal muscle of the colon. Action of prostaglandins at the receptor level is not blocked by atropine **(Horton, 1979),** *they are not neurotransmitters but they modify synaptic function.*

Regarding the effect of prostaglandins on gastric secretion PGEs, PGAs and PGIS inhibit gastric acid secretion stimulated by feeding, histamine or gastrin **(Robert, 1977).** *Volume of secretion, acidity and content of pepsin are all reduced probably by direct action on the secretory cells.*

- *Mucus secretion in the stomach and small intestine is increased by prostaglandins.*

- *P.G.E. stimulates the secretion of water and electrolytes from the jujenum* **(Pierce et al., 1971)** *by increasing intestinal cyclic A.M.P. Simulating cholera toxins, thus using of prostaglandin inhibitors as Aspirin & indomethacin may decrease or inhibit the secretory effects of cholera toxins. Prostaglandin level in stools or in blood are increased in patients with ulcerative colitis* **(Gould et al., 1977).**

Effect on pancreas

- *P.G.E_1 inhibit the secretion of fluid and electrolytes in both the resting gland and that stimulated by secretin or pancreozymin. While increasing the release of pancreatic enzymes* **(Rudick et al., 1971).**

- **Robertson & Chen (1977)** *found that P.G.E. infusions inhibit glucose induced insulin secretion. Salicylates augment both basal and glucose stimulated insulin secretion.*

- *About the effect on alpha cell function it was proved by* **Torolla et al. (1979)** *that prostaglandin E stimulates glucagon secretion.*

Endocrinal & Metabolic Effects

- *PGE_1 and PGFs stimulate the release of ACTH.*
- *PGEs enhance the release of GH.*
- *PGF_2 stimulate the release of prolactin and gonadotrophins.*
- *PGE_2 stimulate the release of (L.H.) and thyrotropin.*
- *It was proved by* **Giugliano et al., (1979)** *that P.G.E. has caused hyperglycaemia, it is not established whether or not this hyperglycaemic effect is related to increased secretion of hormones such as glucagon, cortisol and growth hormone.* **Chen & Robertson (1979)** *discovered that glucose tolerance is either unaffected or improved by drugs that inhibit prostaglandin synthesis with the single exception of indomethacin, the increase in glucose production caused by glucagon has been reported to be diminished by indomethacin.*

- *Parathyroid like effects that result in mobilization of calcium from bone in tissue culture (***Klein and Raisz, 1970).**

III. Prostaglandins and the Lung:

- *P.G.F_2 & have a remarkable pulmonary vaso-constrictor effect while their effect on systemic vascular resistance is insignificant (***Hyman, 1969).**

- *PGF is a bronchioconstrictor while PGE_1 & PGI_2 have a good bronchiodilator effect (***Goodman & Gilman, 1980).**

IV. Cardiovascular System

- *Vasodilatation of arterioles, precapillary sphincters, and post capillary venules.*

- *Cardiac output is generally increased by PGSE, F & A.*

- *Increase force of cardiac contractility is a direct inotropic action, as well as increase heart rate reflexly as a consequence of fall in total peripheral resistance.*

- *Systemic blood pressure generally falls in response to PGS E & A and blood flow to most organs including the heart and kidney* **(Lee, 1974).**

- *Thromboxane* A_2 *is a direct powerful vasoconstrictor substance* **(Sameulsson et al., 1978).**

V. Effect of Prostaglandin on the Blood

PGE_1 *and* PGD_2 *inhibit the aggregation of human platelets,* PGE_2 *exerts variable effects on platelets, it is a potentiator of some forms of aggregation at low concentration and an inhibitor at high concentration. Thromboxane* A_2 *is a very powerful inducer of platelet aggregation, this physiological pathway of platelet aggregation dependent on generation of thromboxane* A_2 *is sensitive to the inhibitory action of aspirin* **(Moncade Andvane, 1978).**

PGA_2, PGE_1 *and* PGE_2 *induce erythropoiesis by stimulating the release of erythropoietin from the renal cortex.* PGE_1 *and*

PGE_2 decrease red-cells fragility at low concentration (10-100 pn) while at higher concentration (1 nm) they increase it **(Rasmussen and Lake, 1977).**

VI. Reproductive System

Earlier studies have demonstrated that PGE and PGF_2 are present in the ovary, fallopian tube, endometerium and myometrium, placenta, decidua, and the amniotic fluid at the onset of labour or spontaneous abortion and are increased in the peripheral circulation during abortion or labour. The human uterus whether pregnant or not is always contracted by PGE_1, PGE_2 adminsterated intravenously. Prostaglandins stimulate the release of luteinizing hormone, induce ovulation and transport of gamete, inhibit the decidual reaction, produce luteolysis late in menstrual cycle, terminate pregnancy, and may initiate parturition **(Clayman, 1975).**

VII. Nervous System

Prostaglandins are present throughout the central and peripheral nervous system, they have potent actions and are released from within the brain and spinal cord by neural and chemical stimuli. The PGS are thought to play a primary role in thermoregulation. PGE; is a potent pyretic, sedative and anticonvulsant properties have also been observed. 'PGF_2' however, has facilitated the experimental induction of convulsions and has occasionally enhanced the response of certain receptors to norepinepherine and potentiated

spinal motor reflexes. Epileptic episodes have been noted in some patients receiving PGF_2 & **(Clayman, 1975).**

VIII. Relation of Prostaglandin to Human Hypersensitivity

Both cellular and humoral immune response are under negative control by prostaglandins, in vivo P.G. synthetase inhibitors result in enhanced delayed hypersensitivity skin test responses and in enhanced cytotoxicity **(Goodwin et al., 1978).**

Highly significant increases in the concentration of $P.G.E_2$ and $P.G.F_2$ were reported in psoriatic lesions as compared to uninvolved skin of the same patients **(Hammarstrom, 1975).** Concurrent studies indicated that synovial fluid of patients with rheumatoid arthritis contains higher concentrations of $P.G.E_2$ and to a less extent $P.G.F_2$ than synovial fluid of subjects with non-inflammatory arthropathies **(Robinson, 1979).**

IX. Relation between prostaglandins and tumours:

It was evidenced by **Pelus and Strausser (1979)** that prostaglandins were feedback inhibitors of normal humoral and cellular immune responses, this normal feedback system is accelerated in some tumour-bearing animals and man, leading to suppressed immunity.

The defect in cell-mediated immunity in hodgkin's disease was caused by circulating suppressor cells which produce prostaglandins **(Sibbit et al., 1978).**