EICOSANOIDS AND ANESTHESIA

ESSAY SUBMITTED FOR PARTIAL FULFILMENT OF MASTER DEGREE IN ANAESTHESIA

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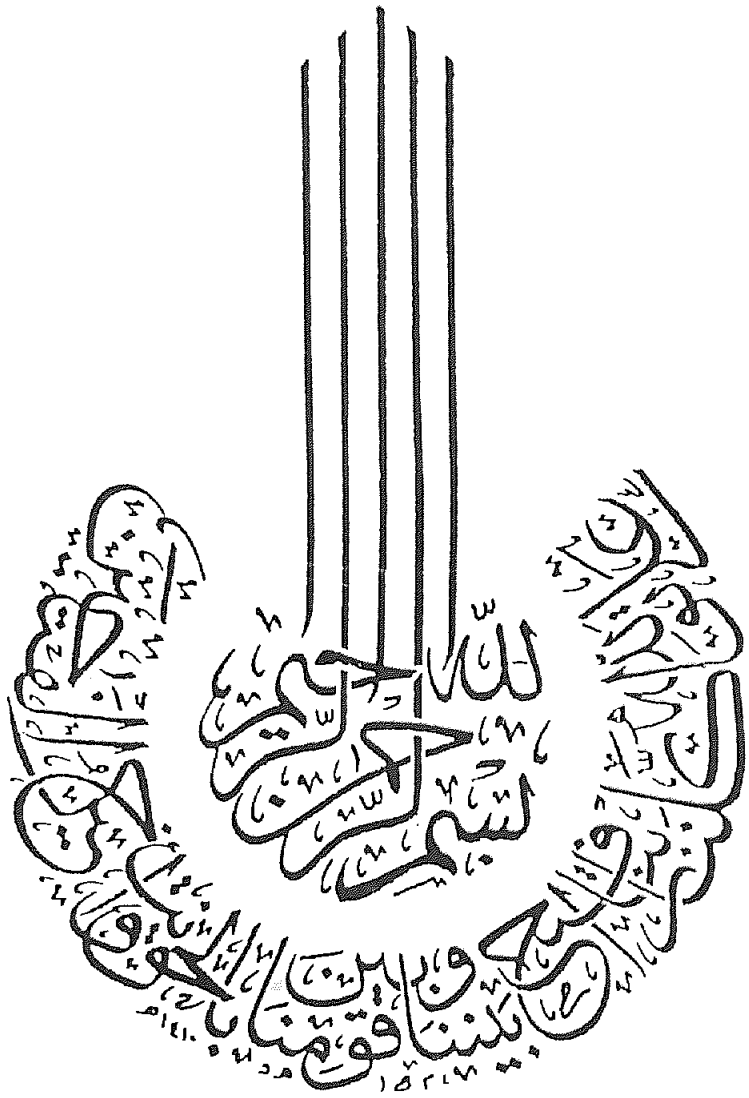

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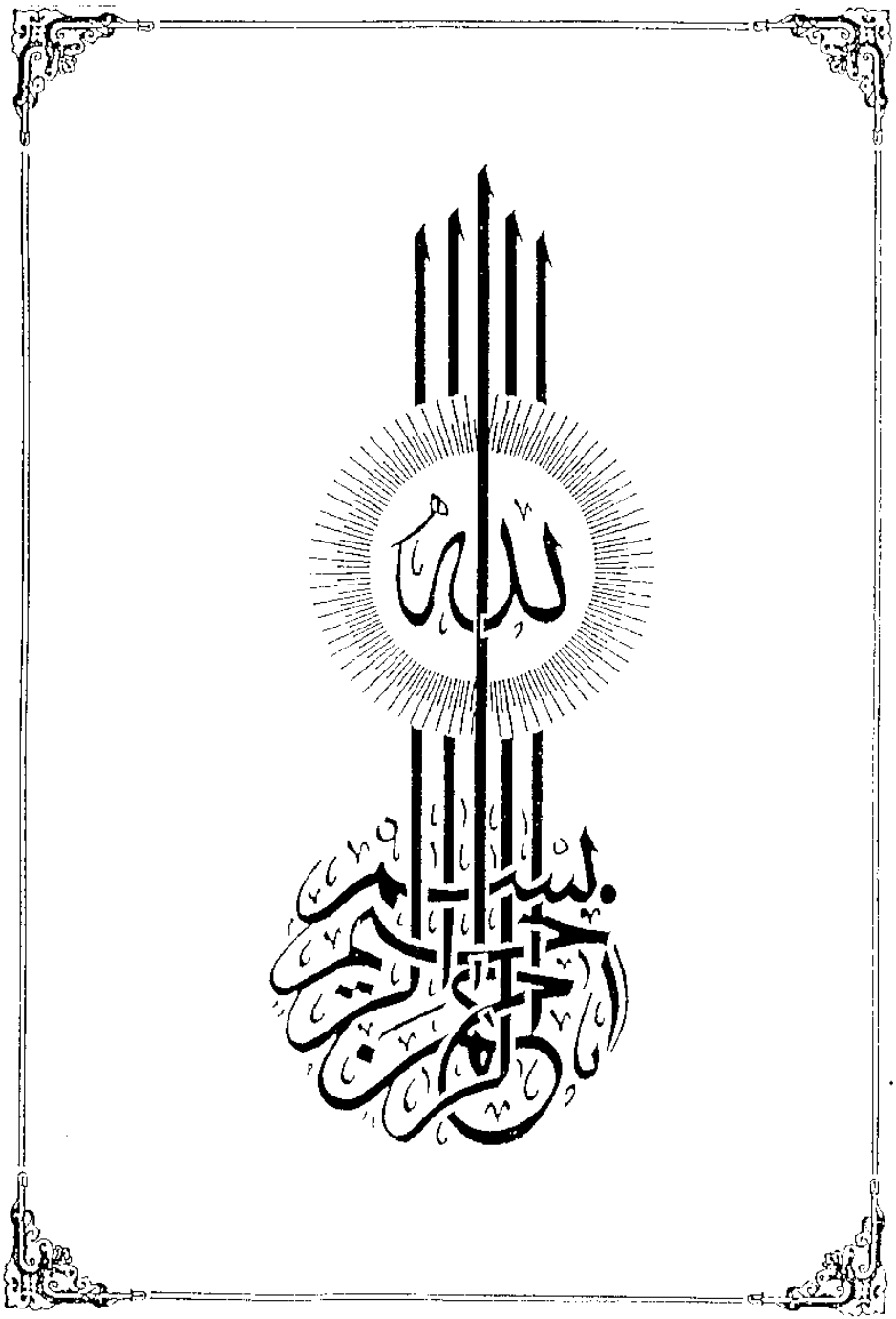

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To

My Family

Nagwa Mohamed Doha

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Nagwa Mohamed Doha

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INTRODUCTION

Introduction

The term eicosanoid is a name for compounds which are derived from acid precursor. Eicosanoids; eicosa 20 carbon; enoic-containing double bonds (**Goldberg et al., 1988**).

The products synthesized from arachidonate vary and include the prostaglandins; thromboxanes; hydroxyeicosatetraenoic acids and the leukotrienes (**Patrono et al., 1986**).

The eicosanoids are intermittently released into the circulation. The active molecules have very short half lives, however, eicosanoids produce profound effects in 10^{-12} pg/ml concentration. They do not have specific target organs, this is unlike the well-known endocrine hormones which have target organ specific, and often present in larger 10^{-6} mg/ml quantities (**Goldberg et al., 1988**).

Although eicosanoids affect many biologic processes, their importance as mediators and regulators of complex cellular functions has only recently been appreciated (**Oates et al., 1988**).

The naturally occurring eicosanoids have only limited therapeutic application, but stable derivatives are valuable therapeutic agents (**Goodman et al., 1980**).

Prostaglandins are naturally occurring compounds composed of a 20-carbon fatty acid and a cyclopentane ring. The molecular skeleton is represented by prostanoic acid (Goldyne, 1987).

Prostaglandins proved to be of great value in medical practice (Crossland, 1980).

History

The history of prostaglandins underscores many of their important properties. In the 1930s, VanEuler in Sweden and Goldblatt in England independently described the hypotensive and smooth muscle stimulating properties of lipid extracts of seminal fluid (Clark et al., 1992).

VanEuler soon recognized that these activities could not be attributed to any known substance. Because he believed that it is originated in the prostatic gland; he named the active substance, prostaglandin. After elapse of more than 10 years (1940s), Bergstrom isolated hydroxy fatty acid fraction from lipid extract of seminal vesicles (Bergstrom et al., 1968). Almost 10 more years passed before he was able to purify from this fraction two components that had the biologic activities attributed to the original extract. They were designated "prostaglandins E and F" (Rang et al., 1993).

Bergstrom and Samuelsson subsequently isolated additional compounds from sheep vesicular gland extracts and identified the pathway for their formation (**Bergstrom et al., 1962**).

The active compounds were derived from oxygenation of arachidonic acid, a precursor released from membrane phospholipids (**Clark et al., 1992**).

A signal achievement was the demonstration by **Vane, Smith** and by **Wills** early in (1970s), that acetyl salicylic acid (aspirin) and related drugs block the synthesis of prostaglandins (**Smith et al., 1971**).

It was proposed that this action might account for the anti-inflammatory and analgesic effects of aspirin. Furthermore, these studies provided a pharmacologic method to determine the role of prostaglandin in physiology and disease (**Van, 1971**).

Thorough studies of the metabolism of arachidonic acid, Samuelsson and coworkers late in 1970s identified two cyclic endoperoxide intermediates (PGG_2 and PGH_2) that are transformed enzymatically into prostaglandins and into a labile, platelet-aggregating vasoconstrictor compound designated thromboxane A_2. Van and coworkers found that in vascular tissue the cyclic endoperoxides are also metabolized to a potent but transiently acting vasodilator. They recognized

that this activity differed from that of known and they attributed it to prostaglandin X (PGX) (**Moncada et al., 1978**).

PGX was produced primarily by vascular endothelium. It also inhibited platelets aggregation, both in vivo and in vitro. When the structure of PGX was determined, it was renamed prostacyclin or PGI_2. For their discoveries in this field, Samuelsson, Bergstrom and Vane were awarded the Nobel prize in physiology and medicine in 1982 (**Clark et al., 1992**).

It is believed that pharmacologic research in eicosanoid biology will provide anesthesiologist with new medications to care for the patient in the operating room and intensive care unit (**Shayevitz et al., 1985**). Refinement in measurement techniques will enable investigator to better understand eicosanoids physiology and pharmacology.

Advances in receptor biology will provide a foundation for the development of more specific, non-toxic, eicosanoid agonists and antagonists (**Coleman et al., 1984**). Clinical trials will then establish efficacy of these new drugs. Tomorrow's anesthesiologist may say "In my practice, I use a medication derived from prostaglandin daily".

CHAPTER 1

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Eicosanoid Biosynthesis

The eicosanoids are among the most potent naturally occurring autacoids, the later is defined as organic endogenous substance with intense pharmacologic activity.

Eicosanoids are becoming increasingly recognized as important cell regulatory substance (**Rosenkranz, 1989**). Other commonly known autacoids include histamine, serotonin and angiotensin (**Goldberg et al., 1988**).

Arachidonic acid synthesis, reacylation and release

Several biologically active lipid and peptidolipid acids are formed from the same precursors as the prostaglandins through interrelated enzymatic pathways (**Malle, 1987**). These other lipids are nearly all carboxylic acids and include the thromboxanes (TXs). The hydroperoxyeicosatetraenoic acids (HPETEs) and hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs) and the more recently discovered lipoxins (LXs) and epoxyeicosatetraenoic acids (EETEs). The general term eicosanoid is used to refer to these compounds because

they can all be derived from polyunsaturated fatty acids with 18-, 20- and 22- carbon skeletons (**Hecker et al., 1992**). Among these fatty acids, arachidonic acid is the most important precursor for the biosynthesis of eicosanoids in humans.

Linoleic, α-linoleic and arachidonic acids are the only fatty acids known to be essential for the complete nutrition of many species of animals including humans. In most animals, arachidonic acid is formed from linoleic acid by desaturation and chain elongation to di-homo-γ-linolenic acid and subsequent desaturation.

However, linoleic and linolenic acids are not synthesized in humans, so, they must be supplied in the diet (**Hecker et al., 1992**).

The precursor fatty acids which are derived from diet, are not free within cells but are esterified in the form of phospholipids, triglycerides or cholesterol ester (**Johnson, 1991**).

Eicosanoids are not stored in the cell, so their biosynthesis is limited by the availability of the free precursor fatty acids.

Arachidonic acid is released from membrane lipids and other lipid esters by phospholipases that are activated by specific and non-specific stimuli (**Fitzpatrick et al., 1989**).

Stimulation could be mechanical distortion of the cell membrane, changes in the ion fluxes, ischemia, hormones and drugs; these can activate tissue phospholipase by a process that depends on Ca^{++} from extracellular and intracellular stores **(Johnson, 1991).**

In response to these stimuli (specific or non-specific) which vary from cell to cell, phsopholipase A_2 or a combination of phospholipase C and diglyceride lipase cleave esterified arachidonic acid from the 2-position of specific glycerophospholipids that make up part of the lipid bilayer of the cell membrane (Fig. 1) **(Vance et al., 1985).**

The amount of intracellular free arachidonic acid is partially controlled by the reincorporation of arachidonate into cellular lipids.

This reacylation is regulated by 2 enzymes : arachidonyl-CoA synthase, which forms the activated coenzyme A fatty acid ester; and arachidonyl CoA transferase, which adds the CoA ester to the 2-carbon of a lysophospholipid **(Ramwell et al., 1980).**

Further transformations in the phospholipid pools may produce 1-alkyl-2-acetyl-lysophos-phatidyl-choline, or platelet-activating factor (PAF) (Fig. 2). The inhibition of any of these enzymes leads to increased intracellular levels of free arachidonic acid **(Hecker et al., 1992).**