Endothelins
in Relation to Anesthesia

Essay Submitted for Partial Fulfillment of Master Degree in Anesthesiology

BY

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***** 1999 *****

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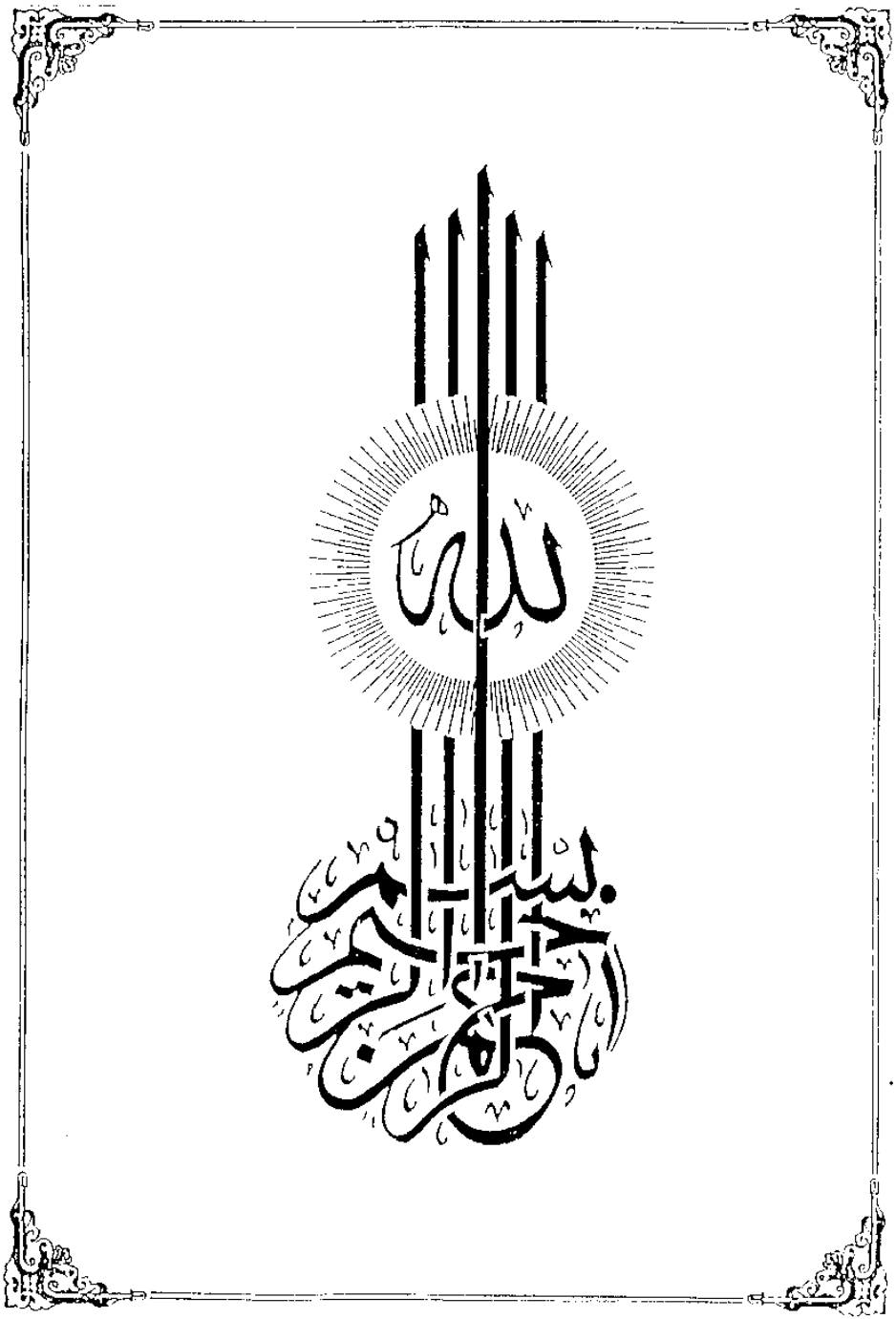

Acknowledgment

First thanks are all due to **God** for blessing this work until it has reached its end as a part of his generous help throughout my life

I would like to express my deepest gratitude to **Prof. Dr. Layla Ali El-Kafrawy** Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University for her great support and continuous encouragement throughout this whole work. It is a great honor to work under her guidance and supervision.

I am truly grateful to **Ass. Prof. Dr. Azza M. Shafik Abd El-Meguid**, Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for her close supervision, sincere help, valuable suggestions and continuous encouragement throughout the whole work.

My deepest appreciation and grateful thanks are due to **Dr. Mohamed A. Hanafy Mahmoud**, Lecturer of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University, for his kind advice, meticulous revision, and his great efforts throughout this work.

Wael Shendy

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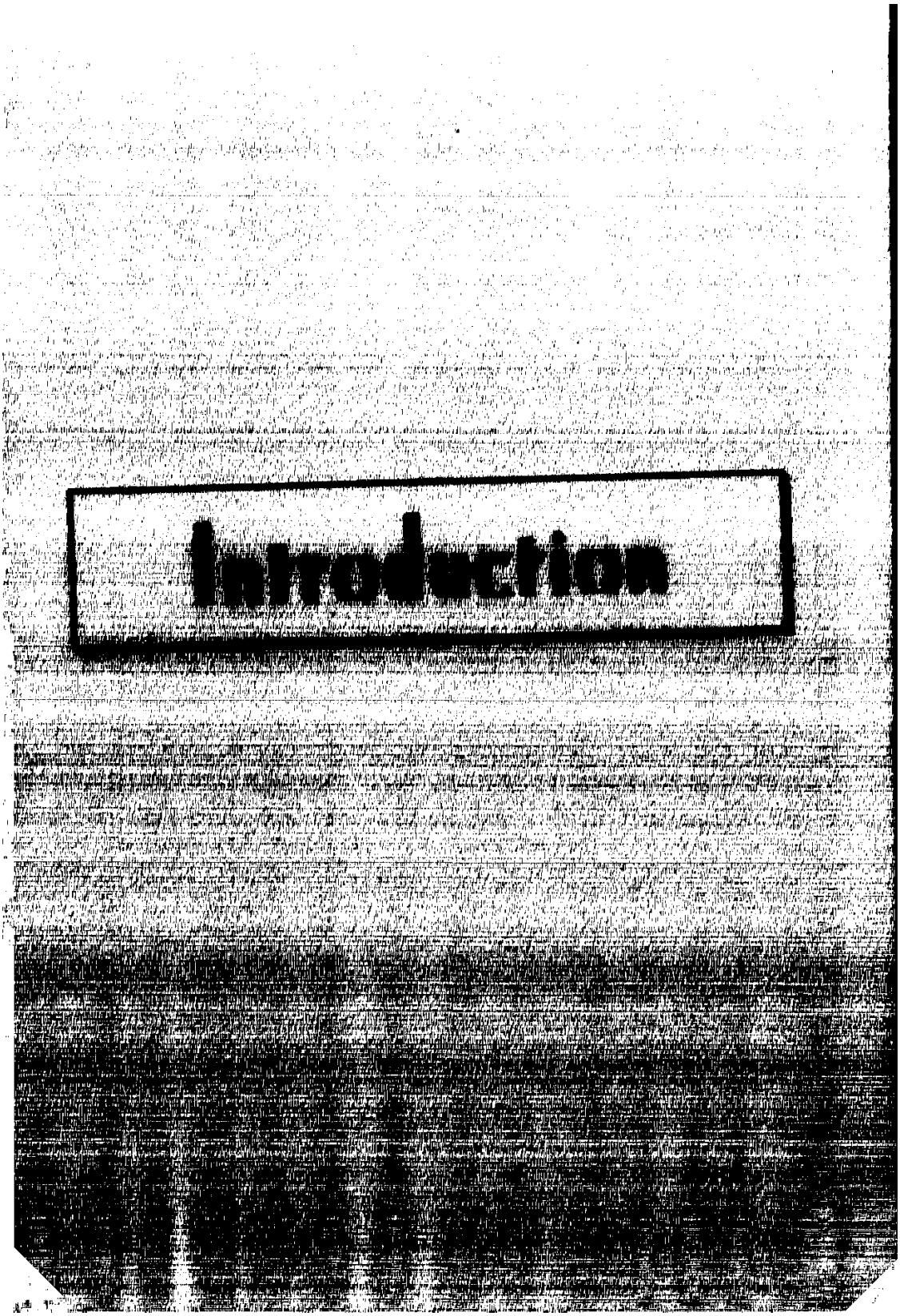

Introduction

The vascular endothelium plays a major physiologic role in the regulation of vascular tone mediated by endogenously synthesized vasoactive substances.

Hickey et al., in ***1985***, described endothelin as endotensin or endothelial contracting factor. It was described as naturally occurring polypeptide substance produced by vascular endothelial cells and has a potent vasoconstrictor and mitogenic activity on vascular smooth muscle cells.

Endothelin is considered as a disease marker or an etiologic factor in pulmonary hypertension, systemic hypertension, congestive heart failure, myocardial and vascular wall hypertrophy, ischemic heart disease, and atherosclerosis ***(Praveen, 1995)***.

Yoshibayashi et al., in ***1991***, discovered that endothelin may be involved in pathophysiology of pulmonary hypertension.

Vincent et al. (1993) suggested that the increase in pulmonary blood flow may be a stimulatory factor in production and/or release of endothelin in children with congenital heart defects.

This was also reported by ***Ishikawa et al.*** in ***1995***, who studied patients with left-to-right shunt. They found significantly higher levels of endothelin in their patients when compared to control subjects.

Endothelin

In 1985 - 1986, three groups of investigators discovered a vasoconstrictor peptide produced by endothelial cell culture or by intact blood vessels subjected to hypoxia, stretch, and by other stimuli ***(Hickey et al., 1985; Rubanyi and Vanhoutee, 1985; and Gillespie et al., 1986)***

It has become apparent that the endothelium of arteries and veins regulate the state of vascular contraction and relaxation ***(Gryglowski et al., 1988)*** The best studied vasorelaxant factors are endothelium-derived relaxing factor (EDRF) as nitric oxide, and prostacyclin like prostaglandin I_2 (PGI_2) which are produced by endothelium, and vasoconstrictor factors such as peptidoleukotrienes and endothelium-derived contracting factor (EDCF) which was suggested to be a peptide ***(Kramer et al., 1992)***

The interest in this vasoconstrictor was heightened in 1988 by ***Yanagisawa and his colleagues*** who reported their description of isolation and purification of cultured porcine aortic endothelial cells which are characterized by having a wide variety of actions on both vascular and non-vascular tissue including vasoconstriction and mitogenesis of the blood vessels This compound was named "endothelin". Three genes have been identified for endothelin in human DNA. The nucleotide sequences of the three human genes are highly conserved within the regions encoding the 21-residue endothelin, one of which is exactly matched to the sequence of

ET-1 exhibits more vasoconstriction than ET-3 ***(Kimura et al., 1988)***.

Source:

It has been found that endothelin is released from many endothelial cells including:

- Porcine aortic cells.
- Bovine pulmonary cells.
- Bovine carotid cells
- Human umbilical veins.

(Kramer et al., 1992)

Endothelin has also been identified in numerous non-endothelial cells including:

- Renal cells.
- Canine airway epithelial cells.
- Neuronal cells.
- Connective tissue cells.
- Tumor cell lines with epithelioid morphology.

(Jankidevi et al., 1992)

Production:

Endothelin isopeptides originate from the proteolytic conversion of "prepropeptides" to the final 21 amino acid product Endothelial cells synthesize a "preproendothelin" (200 amino acids) by mRNA expression which is cleaved to an intermediate form of "proendothelin" or "big endothelin" (39 amino acids). subsequently an endothelin converting enzyme cleaves the big endothelin between trp[21] and valine[22] to form the mature and active form (21 amino acids) ***(Inoue et al,. 1989)*** **(figure 3)**

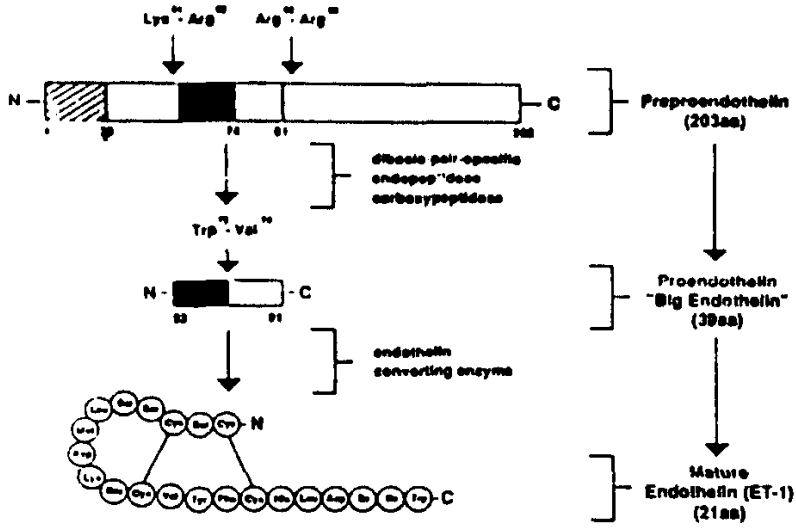

Figure (3): Proteolytic processing of preproendothelin and proendotehlin in biosynthesis of mature ET-1 ***(Highsmith et al., 1992).***

Stimuli for Synthesis:

Some vasoactive substances may control the synthesis and the release of ET in peripheral blood vessels. It is now well known that various factors including thrombin, phorbolester, ionomycin, transforming growth factor beta, interleukin-1, and tumor necrosis factor induce production through mRNA production ***(Maemura et al., 1992)***.

The administration of transforming growth factor beta, ionomycin, arginine and vasopressin into the cultured endothelial cells elicits the release of ET from the cell ***(Masaki et al., 1990)***.

The mechanism of release of endothelin from endothelial cells is usually by the induction of the maximum amount of ET preproform in cultured endothelial cells after the addition of thrombin, this takes 30 minutes or more ***(Yangisawa et al., 1988)***.

Stewart and his colleagues in ***1990*** demonstrated that the production of endothelin in endothelium was markedly reduced in co-culture with smooth muscle cells or fibroblasts, suggesting the existence of some feedback regulatory mechanism in the production of ET. Thrombin stimulates the release of endothelium derived relaxing factor (EDRF) as well as production of ET. on the other hand, the increase in production of ET due to thrombin is inhibited by EDRF ***(Masaki et al., 1990)***.

Calcium ionophore elicits phosphoinositide breakdown, producing 1,2-diacyl glycerol and inositol 1,4,5 triphosphate and increasing free calcium ions, which activates the protein kinase C.

In turn, activation of protein kinase C induces production of ET-1 mRNA *(Masaki et al., 1991)*

"Big ET-1" is probably secreted from the endothelium and converted into ET-1 in the extracellular space. It has been observed that when a bolus of "big ET-1" was administered intravenously, plasma ET-1 level increased slowly and was detected even at 60 minutes after administration. However, a significant increase in ET-1 could be detected for only 5 minutes when ET-1 was administered.

It has been recognized that "big ET-1" is probably slowly converted to ET-1 in the plasma. Likewise, increase in blood pressure following administration of "big ET-1" to its peak at 5 minutes rather than 1 minute as with ET-1, because "big ET-1" is as potent as ET-1 in eliciting the pressor response despite the low vasoconstrictor activity in vitro *(Kimura et al., 1989)*.

These results strongly suggest that "big ET-1" can probably be converted to ET-1 on the surface of endothelium, thus conversion of "big ET-1" to ET-1 may be of physiological importance.

As regards the converting enzymes, there are three functions of endothelial cells have been demonstrated to display converting enzyme activity. Two of these are in cytosolic fractions, and the other is membrane fraction *(Sawamura et al., 1990)*.

The most probable candidate for the converting enzyme is the membrane-bound fraction which is inhibited by EDTA, O-phenanthroline or phosphoramidone *(Ikegawa et al., 1990)*.

This membrane bound neutral "metalloendopeptidase" is more sensitive to "big ET-1" than to "big ET-3". Phosphoramidone specifically suppresses the production of ET-1 from cultured endothelial cells ***(Kitamura et al., 1990)***.

In the vascular endothelium, it may be evident that "big ET-1" is converted to ET-1 in extracellular space; however, in tissues other than vascular endothelium, the conversion mechanism may be difficult as in porcine nervous tissue, "big ET-1" is rarely detected and also low in the kidney ***(Yokokawa et al., 1989)***.

Regulation of Synthesis:

Very little is known about regulation of endothelin genes and hence, synthesis of endothelin in vivo and in vitro. The gene encoding porcine and human pre-pro-ET-1 has been cloned and sequenced. In the pig, analysis of complementary DNA synthesis from pre-pro-ET-1 mRNA revealed that ET-1 is derived from amino acids 53 - 73 of a 208 amino acid pre-pro-ET-1 ***(Itoh et al., 1988)***.

In 1989, ***Bloch and coworkers*** have isolated and sequenced a DNA probe complementary to human pre-pro-ET-1 mRNA. Using this probe to select genomic clones, they determined that the human pre-pro-ET gene contains 5 exons and 4 intros. DNA sequences encoding the mature ET-1 peptide are contained within the second exon. The third exon encodes a portion of prepro-ET-1 that is homologous with the mature ET-1 peptide ***(Inoue et al., 1989)***.