β-ENDORPHIN IN PERINATAL ASPHYXIA

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Dedication

To My Parents,

My Husband

and 2 Sons

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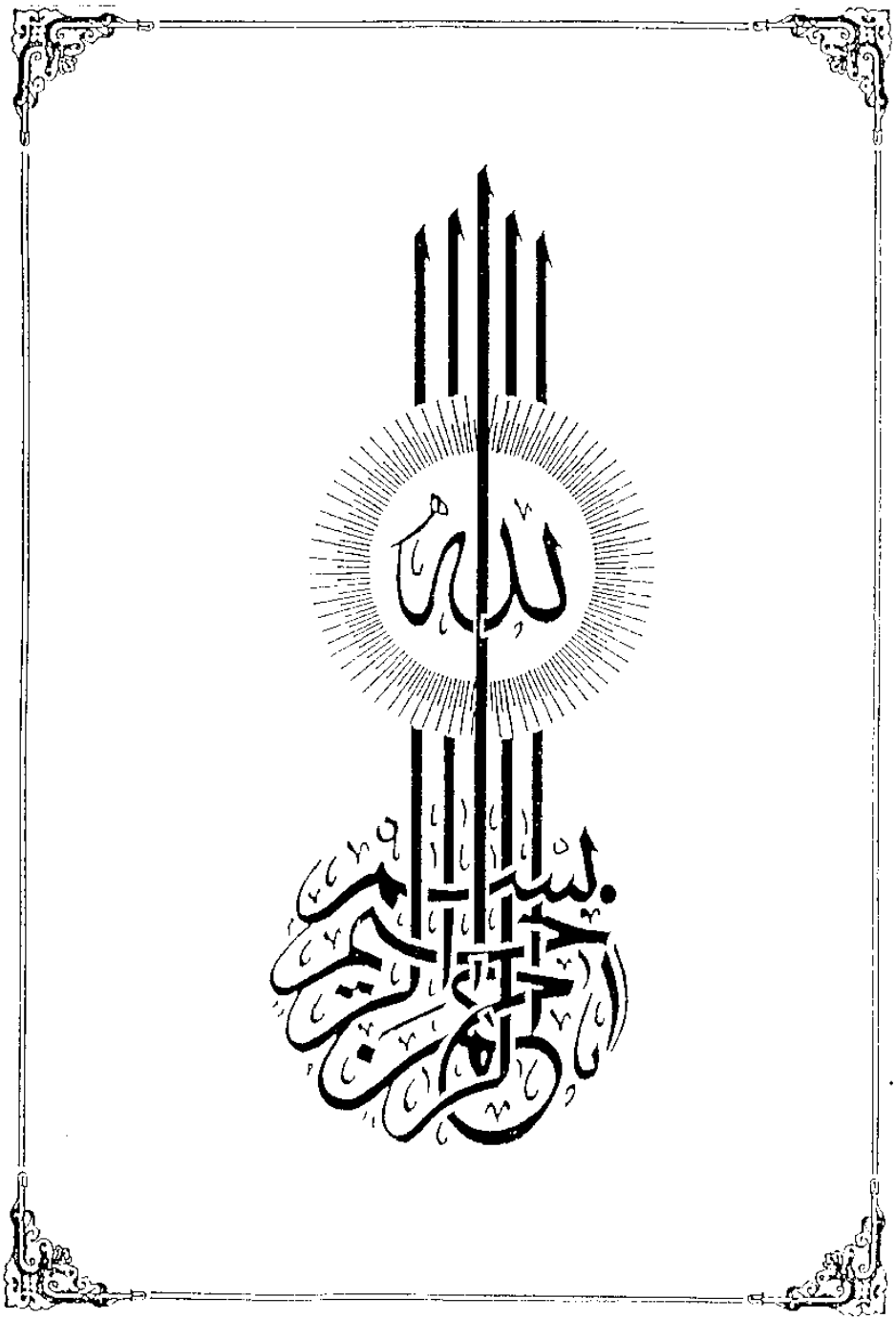

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CONTENTS

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LIST OF ABBREVIATIONS

ACTH	:	Adrenocorticotrophic hormone
β-LPH	:	β-Lipotropin
β-ELI	:	β-endorphin like immunoreactivity
POMC	:	Pro-opiomelanocortin
β-MSH	:	β-melanocyte stimulating hormone
CPM	:	Counts per minute
GAR. PPT	:	Precipitating complex
NSB	:	Non specific binding tubes
C.S.	:	Caesarean Section
DHEA-S	:	Dehydroepiandrosterone sulphide
IUGR	:	Intrauterine gross retardation
F.H.R.	:	Fetal heart rate
FBM	:	Fetal breathing movements
bpm	:	beat per minute

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INTRODUCTION

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INTRODUCTION

β–endorphin is a group of opioid peptide which is derived from β–lipotropin hormone that arises together with adrenocorticotrophic hormone (ACTH) from a common precursor called pro-opiomelanocortin (POMC) (**Mains et al., 1977**).

β–endorphin is highly concentrated in the hypothalamus (**Bloom et al., 1978**), the pituitary (**Guillemin et al., 1977**) and the placenta which has the ability to synthesize it (**Fraioli and Genazzani 1980**).

β–endorphin has been shown to produce a potent analgesia; its pain modulating role has been suggested in stressful situations (**Frederickson and Geary, 1982**) and it has a depressor effect on the blood pressure (**Petty et al., 1981; Kraft et al., 1986 & 1987 and Rossi et al., 1987**).

During labour and delivery, plasma β–endorphin is a measure of stress in the mother and fetus where its concentration rises significantly in response to fetal distress (**Shaaban et al., 1982**).

Hypoxia may be the main stress stimulus in the fetus and opioid peptides in the fetal C.N.S. may act as neurotransmitters that modulate fetal heart rate (**Goodlin, 1987**).

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A significant inverse correlation was found between plasma β–endorphin concentration and PaO_2 and pH (**Wardlaw et al., 1979**).

The physiological effect of this neuropeptide has been recently studied in both animal and human and it was found that it is released in response to insulin induced hypoglycemia, pitressin and metyrapone. It is involved in the central nervous system mechanism regulating pain tolerance and to modulate luteinizing hormone and prolactin secretion also other effects include hypotension, bradycardia and hypoventilation (**Davidson et al., 1987**).

The role of β–endorphin in the regulation of respiration in human neonate is not well understood (**Laungani et al., 1985**). However there is some evidence that perinatal asphyxia or respiratory disturbances in newborn infants are associated with increased activity of this hormone (**Scholle et al., 1990**).

The aim of this work was to study the role of β–endorphin in the pathophysiology of perinatal asphyxia in order to provide the proper management of this important problem in the neonatal period.

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β-ENDORPHIN

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β–ENDORPHIN

Chemistry

β–endorphin is an opioid peptide present in the circulation of man (**Nakao et al., 1979**), and it is the most potent known naturally occurring analgesic agent (**Loh et al., 1976**).

β–endorphin is an opioid peptide formed of 31-amino acid residues (**Bradbury et al., 1976; Loh et al., 1976**) with five amino acid chain that constitutes the met-enkephalin present within its sequence (**Li and Chung, 1976**).

In the pituitary, β–endorphin, β–lipotropin and adrenocorticotrophic hormone (ACTH) occur in the same cells of the anterior lobe (**Wardlaw et al., 1979**). They were found to originate from a multifunctional prohormone by post translational proteolytic cleavage. This prohormone (pro-opiomelanocortin) (POMC) is a common precursor of adrenocorticotrophic hormone (ACTH), α and β–melanocyte stimulating hormones (α, β–MSH), β–endorphin and β–lipotropin (β–LPH) (**Mains et al., 1977; Nakanishi et al., 1979**).

β–lipotropin is a 91-amino acids molecule (**Li & Chung, 1976**) and has no opioid activity (**Kosterlitz and Hughes, 1975**) with the sequence of β–endorphin at its extreme COOH-terminal end (**Loh et al., 1976**).

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β–lipotropin is broken down in a series of steps to β–melanocyte-stimulating hormone (β–MSH), Enkephalin and α, β, γ endorphin **(Kreirger et al., 1980)**.

The principal β–endorphin related peptide in anterior pituitary, are liportropin and β–endorphin 1-31; lipotropin is the major peptide but β–endorphin is produced with a high specificity in its opioid active form. **(Smyth et al., 1982)**.

Synthesis:

Pro-opiomelanocortin, an inactive pre-prohormone is synthesized with ribosomal participation; the endoplasmic reticulum probably involved under the direction of m-RNA, on the membrane-bound polyribosomes, then the cleavage of this sequence from the pre-prohormone on its entry into the Golgi apparatus yields the prohormone **(Hughes et al., 1980)**, then sequential cleavage of the prohormone yields one or more biologically active peptides that are available for secretion **(Docherty and Steiner, 1982)**.

Types of β–endorphin

There are 3 forms of β–endorphin **(Massay and Smyth, 1980)**.

- β–endorphin 1-31
- β–endorphin 1-27
- β–endorphin 1-26

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In human pituitary the principal form of β–endorphin is the biologically potent β–endorphin 1-31, and is accompanied by relatively small quantities of β–endorphin 1-27 **(Smyth & Zakarian, 1982)**.

β–endorphin 1-26 and its acetylated form does not exist in human and generally the acetylated form of β–endorphin might have a non opioid activities **(Smyth et al., 1982)**.

Storage :

Immunoreactivity of opioid peptides is highly concentrated in synaptosomes **(Simantov, 1976)**.

The electron microscopical studies indicate that the opioid peptides are largely concentrated in large granular type vesicles (70-100 nm) **(Höfkelt et al., 1982)**, later the opioids are transported down to the nerve terminals where they are released in a neurotransmitter fashion **(Cuello et al., 1982)**.

Distribution :

β–endorphin, the most potent known naturally, occurring analgesic agent **(Loh et al., 1976)**, was found to be present in the pituitary gland **(Dragon et al., 1977)** and has been shown to be present also in the brain of man **(Swann and Li, 1980)**.

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release in response to stress (**Smith et al., 1981**) and its release is suggested to be under control of corticotrophin releasing factor (CRF) (**Grossman et al., 1982**).

β–endorphin and β–lipotropin are found in cerebrospinal fluid (CSF) (**Terenius & Wahlstrom, 1975**). Jeffcoate et al., (1978) suggested that there are two separate compartments for β–endorphin, the brain CSF which is an important source of β–endorphin and the pituitary plasma.

High proportions of β–endorphin related peptides were present in pancreas and pyloric antrum (**Tanaki et al., 1982**).

Previous studies have demonstrated that circulating β–endorphin is derived, in part, from peripheral sources, such as the gut (**Larson, 1977**) and adrenal medulla (**Boader and Mchardle, 1985**), also it has been demonstrated in human placenta (**Fraioli & Genazzani, 1980**) and in placental tissue fluid (**Kimball et al.., 1981**). Liotta et al., (1982) supported this and reported that cultured human placental cells produce β–endorphin with a post -transitional processing similar to that of human pituitary cells.

Morgioris et al., (1988) demonstrated a high concentration of corticotrophin releasing hormone (CRH) in maternal plasma during pregnancy and showed that human placenta releases

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CRH and pro-opiomelanocortine (POMC) derived peptides (in vitro) which are independent of glucocorticoid control.

Regulation :

The release and synthesis of ACTH and β–endorphin peptides are subjected to corticosteroid feedback inhibition in the anterior pituitary (**Rossier et al., 1980**). Corticosterone acts to suppress both m-RNA synthesis and corticotrophin releasing factor (CRF) (**Grossman and Besser, 1982**).

Injury and stress cause the parallel release of β–endorphin and ACTH via hypothalamic corticotrophin releasing factor (CRF) from anterior pituitary (**Guillemin et al., 1977**).

Similarly, stress activation of sympathoadrenal axis probably leads to parallel release of enkephalin peptide (five amino acid chain that is present within sequence of β–endorphin) (**Li and Chung, 1976**), adrenaline from adrenal medulla (**Livett et al., 1981**): and enkephalin peptides with noradrenaline from sympathetic nerves (**Wilson et al., 1980**).

A various form of stress and conditioning are associated with analgesic states which are either partially or fully reversed by naloxone (**Watkins et al., 1982**).

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