Role of Endorphins and Enkephalins In Pain Disorders

THESIS

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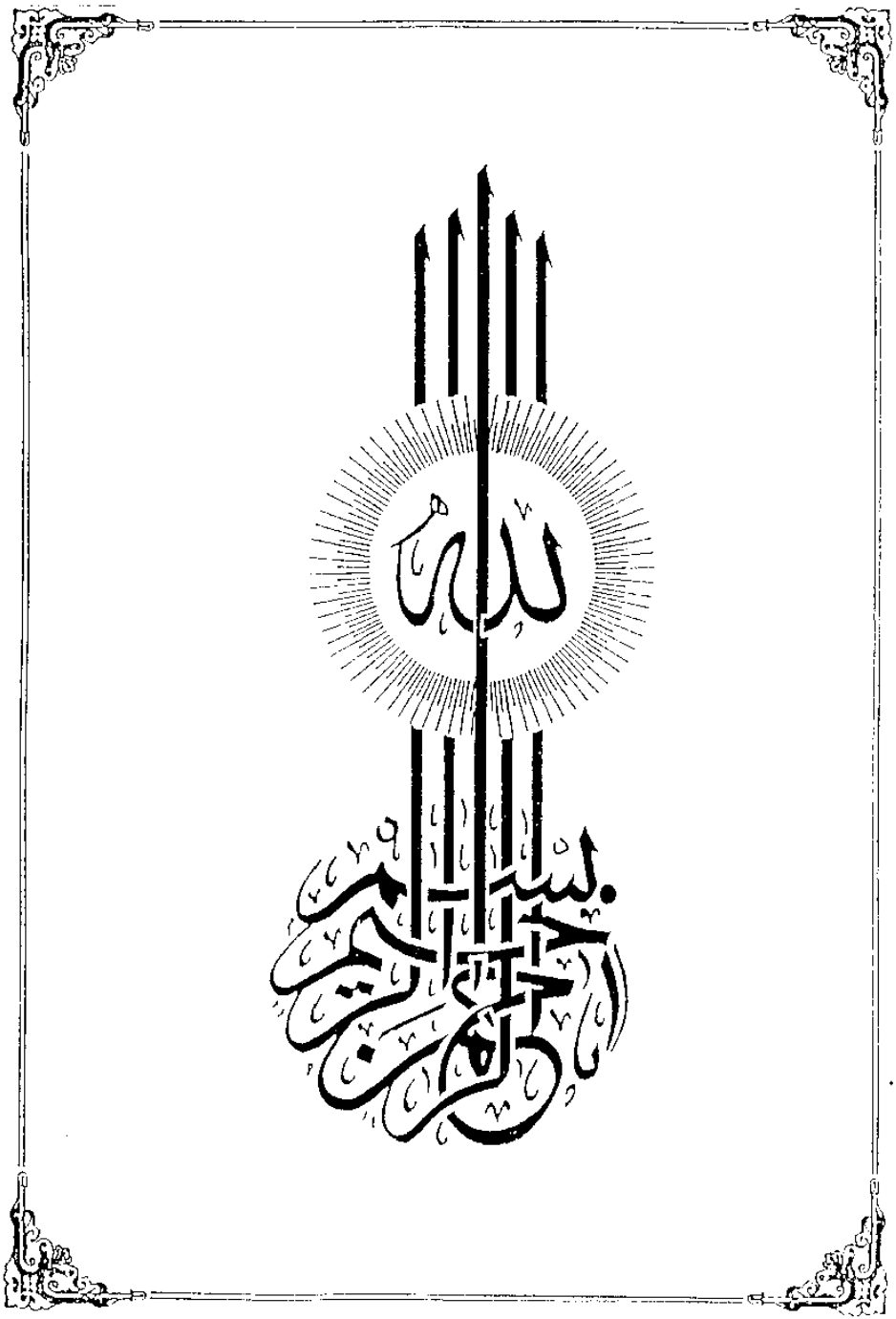
صدق الله العظيم



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INTRODUCTION

The discovery of brain's opioids has been the most widely publicized of the recent advances in neurodchemistry & neuropharmacology. The literature is already enormous & is expanding very rapidly.

The nomenclature may need some clarification.

Enkephalins are pentapeptides & were the first opiate-like to be structurally defined. Endorphins are larger peptides related structurally to beta-lipotrophin. **(Schachter, 1981).**

The enkephalins & ß-endorphins are found in quite different anatomical distribution in mammalian brain. Pro-opiomelanocortin (POMC) - derived peptides (ß-endorphins) are found in large amounts in the pituitary, from which they are released into the blood stream in response to stress, in company with ACTH, Within the brain itself; ß-endorphins are localised to within neurons in the neighbourhood of the arcuate nucleus of the hypothalamus from which long axons project to amygdala, periaqueductal grey matter of mid-brain, locus coerulens & nucleus accumbens. The enkephalins on the other hand; have more diffuse central distributions : being contained largely in shortaxoned neurons. In most neurons metenkephalin is more abundant than leu-enkephalin but the ratio varies considerably from region to region. **(Mackay, 1985).**

In human brain met-enkephalin concentrations are highest in substantia nigra & globus pallidus; with appreciable quantities being detectable in various limbic structures such as hippocampus, hypothalamus, amygdala & cerebral cortex. Outside the brain, the enkephalins are to be found in pituitary, spinal cord, the adrenal medulla, sympathetic ganglia and abundantly in the G.I.T.

The dynorphins are found in detectable amounts in several C.N.S. areas notably the posterior pituiter, spinal cord, hypothalamus and basal ganglia.

The recent stndies have ascertained the valuable role of brain opioids in respect for their predictive role in the success of treatment in some neuropsychiatric disorders (e.g. in a study by **Tonelli et al.,1988**) their role as clinical pharmacological investigations; also their role in explaining the aetiology of some disorders (e.g. a study by **Genazzani et al, 1984**); so playing a very important role in neuropsychiatry as a whole.

In one study; it was proved the derangement of the endogenous opioid system in chronic pain conditions & it was sggested that the ß-endorphin response to SCS (spinal cord stimulation) could have clinical value in predicting the success of treatment, **(Tonelli et al, 1988).**

In another study in migraine sufferers : it was found that the progres sive evolution of migraine is concomiutant with progressive impairment in the C.S.F. levels of ß-endorphins : thus confirming that non-organic central pain is related to a reduced activity of the neurons responsible for the C.S.F. content of ß-endorphins **(Genazzani et al, 1984).**

In a study about vertebral disc diseases; pain factor scores were negatively correlated with the ß-endorphin-like immunoreactivity, indicating a possible role for ß-endorphin in the perception of the severity of pain **(Cleeland et al, 1984).**

There are also other studies dealing with neuropsychiatie disorders as parkinsonism, sehizophrenia, Alzhiemer's disease, depression ... etc., revealing the progressive importance role of opioid peptides in such disorders, **(Mackay, 1985).**

So, spotting light on brain's opioids will be an optimistic view for many patients - those whose life being centred around pain & chronic

illness- as well as for many doctors eagering for more and more medical knowledge about intractable pain disorders so as to practice their precious work in relieving pains of their patients.

Aim of the work :

We are going to shed some light on these points :

1- Relationship between endorphins and enkephalins and various pain conditions.

2- The clinical value of endorphin and enkephalins in predicting the success of treatment in chronic pain conditions.

3- The impairment of endogenous opioids in CSF constitutes an earlier index of non-organic central pain (e.g. migraine) which is related to reduced activity of neurons responsible for CSF content of ß-endorphin.

4- The role of endorphins and enkephalins and their relation to the perception of the severity of pain.

5- Therapeutic uses of endorphins and enkephalins in chronic pain conditions.

(I)

ENDORPHINS AND ENKEPHALINS

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A HISTORICAL BACKGROUND :

Biological assays for the opiates were developed since 1955. The test systems were based on the ability of opiates to inhibit electrically stimulated contractions of the guinea pig ileum and the mouse vas deferens. It was shown that there were strict structural requirements for agonist activity, and that structural modifications of the agonists could produce partial or total antagonists. The concept of the opiate receptor was therefore established **(Schachter, 1981).**

However, the history of oproid peptides started only since **Hughes and his colleagues (1975)** sequenced the pentapeptides met- and leu-enkephelins. But one can consider the years period of 1969-1971 as being the actual beginnings of the field as two totally separate approaches to understand pain and opiates came into existence during those years. One approach was based on observations that electrical stimuli of the periaqueductal grey matter of rats produced analgesia **(Reynolds, 1969).**

This study was followed up leading to the vital discovery that naloxone (the pure opiate antagonist) at least partially antagonized stimulation produced analgesia.

The second approach was biochemical. The criteria for distinguishing between specific and nonspecific opiate binding in brain tissues has been established **(Goldstein et al, 1971).**

Simon et al (1973), Pert and Snyder (1973) and **Terenius and Wahlstrom (1975),** separately reported the next major break through in the field, when the three groups independently reported stereospecific opiate binding in the central nervous system what came to be called *"opiate receptors"*. Since specific opiate binding sites were present in brain; it was logical to assume that an endogenous ligand is present.

In 1975, it has been demonstrated by **Hughes** that brain and pituitary extracts contained opiate like activity and in a rapid series of discoveries, met- and leu-enkephalins were identified **(Hughes et al, 1975).**

In 1976, **Brandbury et al,** reported β-lipotropin (β-LPH) a pituitary hormone containing a 91 amino acid sequence that was shown to have a 61-91 fragment with opiate activity called the "C-fragment" or " β-endorphin".

Also, **Guillemin et al (1976),** isolated two opiate-like peptides from porcine hypothalamus and posterior pituitary termed α-endorphin and γ-endorphin. respectively.

CHEMISTRY :

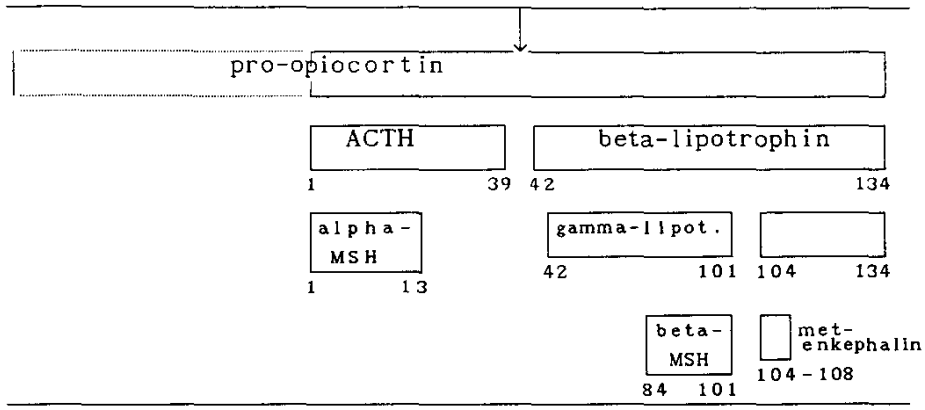
Nomenclature

The commonly used nomenclature for peptides with opiate activity has been a source of confusion. Simon's term 'endorphin' serves to describe all endogenous opioid peptides whereas the term is also used to describe specific individual peptides such as α-, β- and γ-endorphins. A preferable generic term is opioid peptide which is used to describe the general family of peptides with opiate receptor activity **(Mackay, 1985).**

The structural and biosynthetic relationships between many of the opioid peptides is now understood; at least in outline : It is now certain that the lipotrophin-related peptides and ACTH have a common precursor; a glycoprotein with a molecular weight of about 30,000. **(Roberts and Herbert, 1977).**

In a remarkable paper **Nakanishi et al (1979)** have described the messenger RNA nucleotide sequence which codes for this precursor, now usually called pro-opiocortin **(Nakanishi et al, 1979).**

Some of these findings are summerized in the figure below :



Schachter, 1981.

Fig. (1)

This concept of common precursor was supported by immunohistochemical data from normal pituitary tissue which had showed that ACTH (Adrenocorticotrophic hormone), β-lipotrophin (the immediate precursor of β-endorphin) and β-endorphin are all present in the same cells in the anterior and intermediate lobes of the piturtary gland **(Bloom et al, 1977).**

1. Chemistry of Endorphins :

Li, 1964, isolated β-lipotropin from the pituitary gland of sheep and found that it contains 91 amino acids **(Li, 1964).**

Lazarus, Ling and Guillemin (1976); have shown that incubation of β-lipotropin with rat brain extracts generates opioid activity of peptides **(Lazarus et al, 1976).** This finding suggests that β-lipotropin is transient precursor that is readily broken down into β-endorphin.

Guillemin et al (1976) reported that after the discovery of β-endorphin which appeared to be similar to the residue 61-91 of β-lipotropin, subsequently two other fragments with less or different activity were obtained by breakdown of β-endorphin and were named α-endorphin (β-lipotropin 61-76) and γ-endorphin (β-lipotropin 61-77).

In **1980, Gramsch et al** showed that β-endorphin, β-lipotropin and ACTH are synthesized from a common precursor molecule, a glycopeptide with molecular weight of approx- imately 31,000 daltons known as pro-opiocortin which was called previously "Big ACTH". Also, it has been shown that prodynorphin is the precursor of dynorphins **(Mackay, 1985).**

2. Chemistry of Enkephalins :

Haughes and his Coworkers were the first to report the discovery and identification of two related peptides isolated from pig's brain. They named them enkephalins. Both were pentapeptides with similar aminoacid sequence except for N-terminal amino acid. One was called methionine-enkephalin (met-enkephalin) and the other was called leucin enkephalin (leu-enkephalin), according to this N-terminal aminoacid **(Hughes et al, 1975).**

Inspite of the presence of sequence of met-enkephalin within β-lipotropin there is clear evidence that β-lipotropin is not the precursor of enkephelins **(Rees and Smith, 1981).**

The precursor of enkephalins is pro-enkephalin which gives rise to met- and leu-enkephalin, its molecular weight being between 28000 and 32000 daltons. Such precursor with the mother 2 precursors of β-endorphin and dynorphin respectively (i.e. POM = pro-opiomelanocortin and pro- dynorphin) are synthesized under direction by messengerRNA on membrane bound to polyribosomes and whose amino acid sequence was deduced from elegant recombinant DNA analysis of their respective mRNA **(Mackay, 1985).**