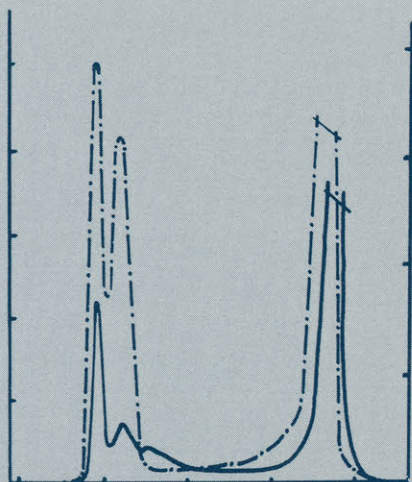


Edited by
Nicholas P. Plotnikoff,
Robert E. Faith, Anthony J. Murgu,
and Robert A. Good



Enkephalins and Endorphins

Stress and the Immune System

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Enkephalins and Endorphins Stress and the Immune System

Edited by

Nicholas P. Plotnikoff

*Oral Roberts University
Tulsa, Oklahoma*

Robert E. Faith

*University of Houston
Houston, Texas*

Anthony J. Murgo

*West Virginia University
Morgantown, West Virginia*

and

Robert A. Good

*University of South Florida
St. Petersburg, Florida*

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FOREWORD

Is this a time for a sleeping giant to rise? We have known since study of the lymphocyte and plasma cells really began in earnest in the early 1940's that the pituitary adrenal axis under intimate control of the hypothalamus could influence immunological functions profoundly. We have also known for at least 20 years in my recollection that female sex hormones can maximize certain immunity functions while male sex hormones tend to suppress many immunological reactions. The thyroid hormones accelerate antibody production while at the same time speeding up degradation of antibodies and immunoglobulins and thyroidectomy decreases the rate of antibody production. Further, much evidence has accumulated indicating that the brain, yes even the mind, can influence in significant ways susceptibility to infections, cancers and to development of a variety of autoimmune diseases. More than 20 years ago, my colleagues and I convinced ourselves, if no one else, that hypnosis can exert major influences on the effector limb of the classical atopic allergic reactions. We showed with Aaron Papermaster that the Prausnitz-Kustner reaction may be greatly inhibited, indeed largely controlled, by post-hypnotic suggestion. And it was not even necessary for us to publish our discovery because scientists in John Humphrey's laboratory at Mill Hill Research Center in London had beaten us to the punch. They described hypnotic control of both the PK reaction and delayed allergic reactions to tuberculin by hypnosis. Although he doesn't necessarily attribute the controls to neurological modulation, I have been convinced that the extraordinary rhythms Franz Halberg in Minnesota has elucidated for immunological functions that range from NK cell activity to the amount of antibody produced and even the tempo of allograft rejection reflect neuroendocrinological interactions with the immunological systems.

Halberg's Chronoimmunologic analyses have been underway for at least 20 years and would have begun earlier and progressed even more rapidly than they have had we immunologists been more responsive to his prodding and that of other chronobiologists associated with him.

Why then does the present moment strike me as so propitious a moment for a comprehensive new work considering the interaction of the major body networks?

For me, a new and truly golden age of psychoneuroimmunoendocrinology began when Wybran of Brussels first observed in 1979 that met-enkephalin

can talk to lymphocytes directly and its conversation with lymphocytes can be interrupted by naloxone. These rather crude beginnings have now been greatly refined and we know for sure that lymphocytes have receptors for met-enkephalin and have either surface or cytosolic receptors for a number of other hormones and neurohumoral mediators. We see in this volume and in numerous contemporary articles reaching our scientific journals that met-enkephalin, leu enkephalin and endorphins can reproducibly influence cell surface expression and functions of lymphocytes in vivo, antibody production, delayed allergic reactions and development and differentiation of lymphoid cells. We are even witnessing these days the first descriptions of responses of immunoparameters in healthy humans and patients with various kinds of immunodeficiencies including patients with AIDS and cancer. All this is happening right now and this science and this form of immunopharmacology will be rapidly developed in the years ahead.

But this is only one of many many exciting fields in psychoneuro-immunoendocrinology where incredible discoveries are turning up.

As a Visiting Professor at the University of Texas Medical Branch in Galveston last winter, I was introduced to a constellation of related studies by Blalock and his group of young colleagues. These studies established to my satisfaction that lymphocytes, like pituitary cells, can produce a molecule very like ACTH both immunologically and functionally and that like cells of the anterior pituitary, the lymphocytes have cytosolic receptors for cortisol. Through these, cortisol can suppress production of the ACTH-like molecule by these cells. As a classical cellular immunologist such a turn of events could never have entered my mind yet here it was, big as life, and it had been demonstrated by what seemed to me to be commanding and critical scientific methodology.

But these surprises are at least paralleled as surprises presented by Hall and Goldstein's (Washington) discovery that thymosin α_1 now a fully defined molecule (thymic hormone?) exerts functional and electrical influences on certain hypothalamic nuclear cells that can, in turn, exert influences on lymphoid cell function through the thymus. If these descriptions sound fanciful it is because I believe they are. Yet they and much, much more are presented in detail in this volume of collected multi-authored papers that reflect a burgeoning scientific field. Even Robert Ader and Nicholas Cohen's exciting discovery that the immune response can be regulated by taste via prior conditioning in the conditioned-aversion response after simultaneous exposure to a cytotoxic immunosuppressive chemical may before long be explained in precise immunopharmacological terms. I now would bet it will.

This field is developing more rapidly than I thought could ever be the case and I am thankful to the immunopharmacologists like Plotnikoff, Wybran, Hadden, Szentivanyi and others who have urged me to pay close attention.

Robert A. Good, M.D., Ph.D.

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INTRODUCTION: YING-YANG HYPOTHESIS OF IMMUNOMODULATION

N.P. Plotnikoff, A.J. Murgo, R.E. Faith, and R.A. Good

Oral Roberts University School of Medicine
Tulsa, Oklahoma

Originally the inspiration for this book stemmed from a Symposium on Enkephalins; Endorphins: Stress and the Immune System held at the Annual meeting of the American Society of Pharmacology and Experimental Therapeutics in Philadelphia 1983. Since that meeting a significant increase in research has occurred and prompted us to compile this book. Recent research has shown that the immune system is exceedingly sensitive to the effects of enkephalins and endorphins. This sensitivity was illustrated by the immunodepressant effects of morphine on T-cells. In contrast the enkephalins and endorphins have shown to enhance T-cell function.

At the same time a major development in this field was the discovery that the adrenal glands are the source of peripheral enkephalins and endorphins. Two major prohormones have been identified in human adrenal glands, namely, Proenkephalin A as well as proopiomelanocortin hormone.

These prohormones have been shown to release various intermediate peptide fragments (Peptide E and F) as well as the final end products, methionine enkephalin, leucine enkephalin, and beta-endorphin. Since morphine is immunodepressant and is found to have high affinity for the mu and kappa receptors, it was of great interest to find that several of the prohormone peptide fragments also has a high affinity for the same receptors, suggesting that they may also have an immuno-depressant role. In contrast the final end products methionine enkephalin and leucine enkephalin and beta-endorphin have been discovered to be immuno-stimulant and bind preferentially to the delta and epsilon receptors.

This immunomodulation by prohormone peptide fragments and enkephalin-endorphin end products led to the Ying-Yang hypothesis of immunomodulation of T-cell function. We are proposing the working opioid peptide hypothesis that various prohormone fragments are released by different stressors resulting in fluctuations of immunomodulation in concert with the steroid hormones and the catecholamines from the adrenal glands. It is possible that a number of contradictory behavioral studies reported in the literature are a result of this immunomodulation (depression and/or stimulation) as a function of differential prohormone processing and type of duration of stressors.

It is intriguing to consider the possibility that long term stress may result in "depletion or exhaustion phenomenon" of prohormone end products (enkephalins-endorphins) depending upon the state of behavioral coping.

Perhaps 'replacement therapy' with the enkephalins-endorphins would be appropriate in certain selected clinical conditions.

Finally, very recent studies indicate that methionine enkephalin stimulates the production and release of lymphokines(interferons and interleukins) from macrophages and T-cells. Therefore, the clinical effects of methionine enkephalin in enhancing T-cell subsets in Kaposi's sarcoma, AIDS, and lung cancer patients may be of therapeutic interest(chapters at the end of the book).

We invite the reader to join us in studying the phenomenon of prohormone fragments released by stress as they impact on the immune system.

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CANDIDATE OPIOID PEPTIDES FOR INTERACTION WITH THE IMMUNE SYSTEM

Christopher J. Evans, Elizabeth Erdelyi, and Jack D. Barchas

Nancy Pritzker Laboratory of Behavioral Neurochemistry
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Stanford, CA 94306

Endogenous opioids are a recently discovered group of peptides which have been implicated as modulators of a number of biological systems. Both opiate receptors and their peptide ligands are widely distributed throughout the CNS and are additionally located in some peripheral sites. The classical effects of opiates as analgesics have perhaps overshadowed many other important biological activities of this group of neuroactive peptides. This book provides strong indications that endogenous opioid peptides play a crucial role in the regulation of the immune system.

Many studies have shown that various stressors have dramatic effects on the functioning of the immune system. The question then becomes one of dissecting out individual components released on the stressful stimuli and determining which may be responsible for the observed changes in immunity. There is a large literature on the effects of glucocorticoids on suppression of the immune function (see Munck et al., 1984 for review). Furthermore, adrenaline has been shown to affect the immune kinetics (Depelchin and Letesson, 1981). A clue that opioids may influence immune responsiveness was indicated in early clinical studies of immuno deficiencies in heroin addicts (Brown et al., 1974). Recent work has shown that opioid peptides can modulate a number of cell types involved in the immune response, and these activities are the subject of other chapters in this book. This chapter will be concerned with the various forms of opioid peptides found in tissues actively secreting into the blood in response to a stressful stimulus, since it is these peptides that will be available for interaction with components of the immune system. Special emphasis will be placed on the opioid peptides that are present in the adrenal gland.

Opioid peptides are generated by enzymic processing of large precursors which themselves are not opiate active. Three opioid precursors have thus far been described: proopiomelanocortin (POMC or pro-ACTH-endorphin); proenkephalin (proenkephalin A), and prodynorphin (proenkephalin B or proneoendorphin/dynorphin). The cDNA representing the messenger RNA encoding the structure of all three opioid precursors has been cloned and the primary amino acid sequence deduced from the cDNA sequence (Nakanishi et al., 1979; Noda et al., 1982; Kakidani et al., 1982; Comb et al., 1982). The endogenous opioid peptides that have been isolated from various mammalian tissues all have at their N-termini

an opiate core sequence: Tyr-Gly-Gly-Phe[met or leu]. The primary structure of POMC contains one opioid core sequence, proenkephalin contains seven, and prodynorphin three. The chemical and spatial integrity of certain features of this sequence are crucial for opiate activity. One essential component is the ionizable amino group at the N-terminus of the opioid core sequence in a particular spatial arrangement to the side chain of the tyrosine residue. Removal of the N-terminal positive charge by acylation of the α -amino group completely obliterates opiate-like properties of these peptides (Bradbury et al., 1977). Therefore, if the α -amino group of the opioid core sequence is engaged in a peptide linkage as in the precursor structures, or α -N-acetylated--a modification found in some tissues, the opioid core is completely inactivated. The N-terminal tyrosine residue of every opioid core sequence is preceded in the three precursors by paired basic residues and in all but one core sequence found in bovine proenkephalin this is a lysyl arginine (see Fig. 1). Cleavage of the precursor at the paired basic residues preceding the opioid core is a prerequisite for the generation of peptides with opiate-like properties. Nature has used paired basic residues as precursor processing signals for the generation of many bioactive peptides (see Steiner et al., 1974 for review). In addition, many precursors are cleaved at single arginine residues (Rehfeld, 1981; Roth et al., 1983). If all paired basics and single arginines were precursor processing sites, the opiate-active peptides would be from POMC, β -endorphin(1-27); from prodynorphin, 3 copies of leu-enkephalin; and from proenkephalin, 6 copies of met-enkephalin and one 1 copy of leu-enkephalin. However, in most tissues, complete processing does not occur such that there are whole consortium of peptides with the opioid core at the N-terminus and various C-terminal extensions. It is interesting that the extent and nature of processing can be variable between tissues, an issue addressed in detail later in this chapter. Figure 1 shows the structure of the three opioid precursors and the endogenous biologically active peptides that have been characterized in various mammalian tissues (see Weber et al., 1983b for review).

The importance of the C-terminal tails following the opioid core sequence should not be understated. The tails infer selectivity for various receptor types, provide stability against exopeptidase attack (Austen et al., 1979), and can influence both the on and off rate of receptor/effector activation. These properties may be crucial when considering an opioid peptide as a candidate for interaction with the immune system. It should, however, be remembered that all endogenous opioid peptides are pure agonists for all receptor types and the micro-environment where the peptides are released and act can be a crucial factor with regard to issues relating to the importance of receptor selectivity and ligand stability.

Identification of Precursor Products

The tissue distribution and concentration of various processing products of the three opioid precursors can be studied using specific antisera as probes. Since all endogenous opioids have a common component at the N-terminus--the opioid core sequence--these specific antisera have to be directed to the C-terminal tails of the various products. As nature would have it, rabbits will indeed direct their antigenic response to the C-terminus of short peptides when certain injection protocols are followed (Weber et al., 1982b). Consequently, antisera can be readily raised which differentiate between the processing products. Often it is possible to obtain antisera that require the C-terminal amino acid as part of the antigenic site. A good example is an antisera we raised to dynorphin(1-8) which, when

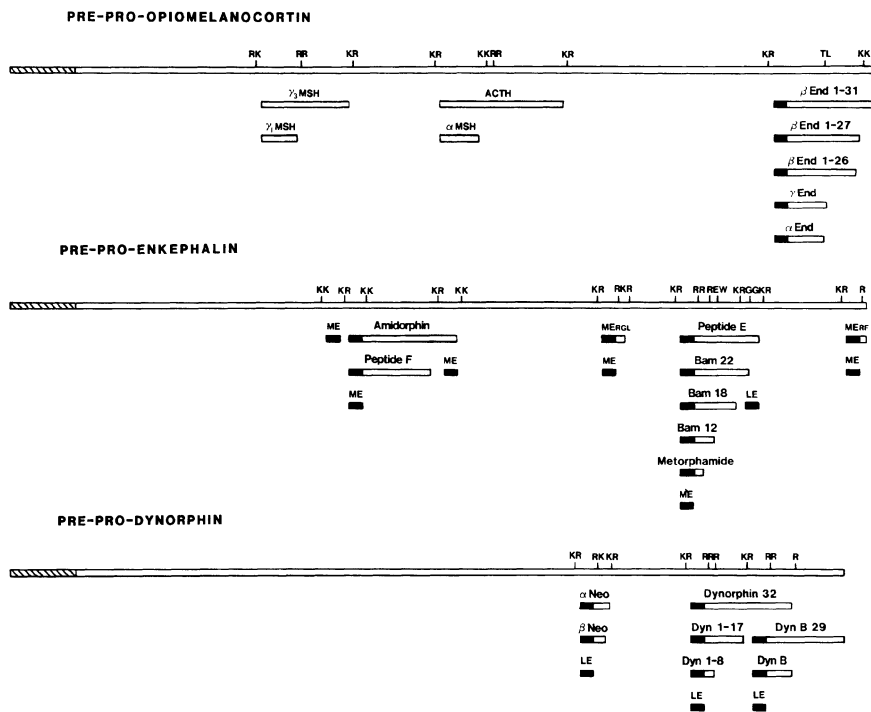


Fig. 1. A large number of endogenous bioactive peptides have been isolated and characterized from POMC, proenkephalin, and prodynorphin. This figure shows the molecular origin of these peptides. The opiate active core sequences are represented by solid bars () and the putative signal regions of the precursors by thatched bars (). The following abbreviations have been used: MSH, melanocyte stimulating hormone; ACTH, adrenocorticotrophic hormone; End, endorphin; ME, met-enkephalin; LE, leucine-enkephalin; Neo, neoendorphin; Dyn, dynorphin; R, arginine; K, lysine; T, threonine; L, leucine; E, Glutamic acid; W, tryptophan; G, glycine; and F, phenylalanine. The structures are for bovine pre-pro-opiomelanocortin, bovine pre-pro-enkephalin and porcine pre-pro dynorphin.

used in radioimmunoassay, has less than 0.1% crossreactivity with dynorphin(1-7) or dynorphin(1-17). Radioimmunoassays using such specific antisera have proven to be an invaluable quantitative tool in the study of endogenous opioid peptides. These assays are quick, sensitive and reliable, although extreme caution must be taken when measuring in tissues such as blood and CSF where interfering substances causing displacement can be mistaken for the presence of peptides. It is advisable in these cases that RIAs be validated by chromatographic analysis of the immunoreactive material. Chromatography of immunoreactive peptides can also reveal different forms containing the same antigenic site. A common problem encountered is that most antisera raised to β -endorphin also recognize the opiate inactive precursor β -lipotropin. Gel filtration chromatography rapidly distinguishes between these two immunoreactive forms. The antisera can also be used for immunocytochemistry which provides precise localization of cells producing a particular opiate peptide. The analysis of opioid processing products by immunocytochemistry in combination with radioimmunoassays has proved to be very powerful and enabled the

construction of detailed maps of the various opioid precursor products in mammalian tissues.

Opioid peptides are found in many peripheral sites that secrete into the blood stream and, consequently, could be available for activation of opiate receptors on cells concerned with the immunoresponse. The presence of β -endorphin-like immunoreactive peptides in the subpopulation of macrophages is of considerable interest in this regard (Lolait et al., 1984). If this β -endorphin-like immunoreactivity proves to be opiate active, an autocrine-like role can be postulated since opiates have been shown to stimulate the IgG mediated antibody-dependent cytotoxicity of macrophages (Foris et al., 1984). Opioid peptides are also present in high concentrations in the pituitary and adrenal glands. Both these endocrine tissues are activated during stress and warrant special attention with regard to their opioid content.

THE PITUITARY

Opioid peptides can be found in all three lobes of the pituitary gland. In the posterior lobe of many species, prodynorphin derived peptides are costored and probably coreleased with vasopressin (Martin and Voigt, 1981). In the oxytocin cells of rat there is immunocytochemical evidence for costorage with met-enkephalin (Martin et al., 1983). In the anterior lobe of the rat pituitary, prodynorphin derived peptides can be detected by radioimmunoassay and there is evidence that these peptides are stored in the gonadotropic hormone secreting cells. More relevant to the theme of this chapter is the β -endorphin-like peptides costored with adrenocorticotropin hormone (ACTH) in the anterior lobe. Proopiomelanocortin has within its structure both the sequence of β -endorphin and ACTH (see Fig. 1). The processing pathway in the anterior lobe of the pituitary is geared for the production of ACTH which is flanked at both the N-terminus and C-terminus by lysyl arginines. The cleavage of POMC at the C-terminus of ACTH leaves β -LPH a fragment of the precursor which contains the β -endorphin sequence yet is not opiate active. This peptide has been shown to be a major product of POMC in the anterior pituitary (Liotta et al., 1978). β -Endorphin (1-31), a very active opioid peptide in many bioassays, is also a product of POMC found in anterior pituitary extracts.

The intermediate lobe of the pituitary contains very high concentrations of POMC-derived peptides. Greater than 90% of the endorphin-like immunoreactive material in rat pituitary is present in the intermediate lobe. It has been demonstrated that certain stressors can stimulate release of the endorphin material not only from the anterior lobe of the pituitary but also the intermediate lobe (Przewlocki et al., 1982). However, the POMC products are very different in the two lobes. More complete processing of POMC occurs in the intermediate lobe than in the anterior lobe such that the major bioactive product of the ACTH portion of POMC is α -MSH--the N-terminal fragment of ACTH, acetylated at the N-terminus and amidated at the C-terminal valine. The endorphin portion of the precursor follows a similar processing pattern. The major products are extensively processed at all paired basic residues and then α -N-acetylated at the N-terminal tyrosine (see Table 1). As previously discussed, the α -N-acetylation is an important modification since it completely obliterates the opiate-like properties of this peptide (for reviews, see Eipper and Mains, 1980; O'Donohue and Dorsa, 1982). The question of why a tissue would synthesize an opioid precursor, then prior to release deactivate the opioid core remains unsolved. Perhaps the MSH portion of the precursor is the important bioactive product or else the acetylated endorphins in the pituitary have an as yet undiscovered nonopioid role.