American Handbook of Psychiatry

The Endorphins and Psychosis

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Introduction

The list of neurotransmitters or neuromodulators has grown enormously in the last few years. Yet, few of these newly discovered brain messengers have so rapidly affected behavioral sciences and biological psychiatry as have the endorphins. Clearly, the thought of having our "own natural opiates" is fascinating and carries more obvious connotations to the psychiatrist than the discovery of other substances with fewer pharmacological ramifications. After all, opiates clearly alter mood and affect, and some of them produce hallucinations and bizarre thought content. They have been occasionally used as therapeutic tools in the past, with varying success. Furthermore, addiction to morphine or heroin is a psychiatric and social problem which presents multiple questions as to its psychological versus its physiological roots and manifestations. Finally, morphine, codeine, and other analgesics on the one hand, and heroin and other "street" opiates on the other, are closely associated in many minds with notions of pleasure and pain—notions that lie at the core of many psychological theories of normal and abnormal behavior.

It is fortunate that the endorphins are so intrinsically appealing, because

they are also complex, numerous, and sometimes frustrating. In the last few years we have learned a great deal about them and from them. While they have yet to provide a key to understanding psychosis, they have taught us a great deal about brain-pituitary relationships, about the nature of neurotransmission, and peptide biosynthesis. They hold some hope for a better understanding of psychosis, an understanding which should be based on sound knowledge of the underlying physiology.

This chapter begins with a presentation of the important basic science issues associated with the field of the endorphins, followed by a discussion of the clinical studies on endorphins, and ends with a summary and discussion of the possible relationships between endorphins and psychosis. The goal of the basic science section is to emphasize the complexity and diversity of endorphin systems in the brain. A clear understanding of the basic science issues is necessary before it is possible to appreciate potential etiological and pharmacological relationships between the endorphins and human psychopathology. In the second section, on clinical theory and data, it is hoped that the reader will utilize the perspectives obtained from the basic science discussions and, in doing so, be able to evaluate the many problems clinical investigators face in attempting to apply this information to the study of human psychosis.

Throughout this chapter, we shall use the terms “endorphin” and “opiate

peptides" interchangeably to denote the whole class of naturally occurring substances that possess opiate-like properties. Terms such as enkephalin, β-endorphin, a-endorphin, or dynorphin all denote specific peptides with known structures that are members of the "endorphin" class (see table 1-1).

Basic Science Studies On the Endorphins: A Summary

The study of endorphins has been very fast paced and has an extremely broad and complex base. Not only have there been a large number of published papers involving the several opiate peptides, but the types of research carried out have been complex, involving every level from electron microscopy and DNA cloning to clinical studies of schizophrenia. Therefore, this discussion will attempt to compress the salient points, in order to give the reader a basis for following the discussion of the possible role of these substances in psychosis.

Opiate Receptors and Stimulation Produced Analgesia

The advent of the field of endorphins can be traced to two main lines of work which came to fruition in the early 1970s. Classical pharmacology, and with it, the preparation of opiate agonists and antagonists in active and inactive stereoisomer forms, was an enormous impetus to opiate research. When this pharmacological armamentarium was combined with the

availability of techniques for producing drugs tagged with radioisotopes, it was possible to demonstrate the presence of specific binding proteins ("receptors") in the mammalian brain to both plant and synthetic opiates. These binding sites were characterized by several laboratories as possessing high affinity for opiates, as being stereospecific, and as being heterogeneously distributed across brain regions and other body tissues. Most importantly, the affinity with which a drug bound to these sites predicted with good accuracy its clinical effectiveness as an opiate. Based on such evidence, it was reasonable to conclude that these membrane sites represented the recognition locus for opiate action and were specific opiate receptors.

At the same time, several investigators at the University of California at Los Angeles were able to demonstrate that electrical stimulation in the brains of rats, and eventually of cats, monkeys, and humans, was capable of producing a substantial degree of analgesia for both acute and chronic pain. This phenomenon is referred to as stimulation-produced analgesia (SPA). These investigators were able to show that the analgesia so produced did not interfere with normal function over a broad set of measures, that it did provide excellent pain relief, and that it was in part reversible by the opiate antagonist naloxone. The ability of naloxone to partially reverse stimulation-produced analgesia (SPA) led to the conclusion that the stimulation released an endogenous material that appeared to be acting on the opiate receptor to produce pain control. In effect, the demonstration of the opiate receptor

by(CH. 1) *The Endorphins and Psychosis* 5 binding techniques and the stimulated release of endogenous opiates through electrical means, taken together, were interpreted by several groups as being strong evidence for the existence of an endogenous opiate peptide system in the mammalian brain.

Table 1-1 Opioid and Related Peptides

Methionine-Enkephalin (Met-enkephalin)	Tyr-Gly-Gly-Phe-Met (β-LPH 61-65)
Leucine-Enkephalin (Leu-enkephalin)	Tyr-Gly-Gly-Phe-Leu
β-Endorphin (β-END)	β-LPH 61-91 (See Fig. 1)
β-Lipotropin (β-LPH)	91 Amino Acids—Contains β-END (See Fig. 1)
Adrenocorticotropin (ACTH)	39 Amino Acids (See Fig. 2)
a-Melanocyte Stimulating Hormone (a-MSH)	Ac-Ser-Tyr-Ser-Met-Gly-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH (See Fig. 2) Cleaved from ACTH and Processed Further
Corticotropin-Like Intermediate Lobe Peptide (CLIP)	(See Fig. 2) Cleaved from ACTH
Dynorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys . . .

Enkephalins and β-Endorphin

Within a relatively few years after these two discoveries, the pentapeptides methionine- and leucine-enkephalin (met- and leu-enkephalin) were extracted from the brain and sequenced by Hughes, Kosterlitz, and their

collaborators (see table 1-1). These two opiate peptides were found to exist in a large number of mammalian brain regions and appeared to agree generally with the distribution of opiate receptors. In their paper describing enkephalin sequences, Hughes and his collaborators pointed out that the structure of met-enkephalin appeared within the longer pituitary peptide β-Lipotropin (β-LPH). Several groups simultaneously recognized that the C-terminal portion of β-LPH, that is β-LPH 61-91 (see figure 1-1), which contained met-enkephalin (position 61-65), could very well be an active opiate in its own right.'' It carried the name C fragment of lipotropin or, eventually, β-Endorphin (β-END). Thus, within a few months we were faced with the existence of not one but three endogenous opiate ligands in mammalian brain (met-enkephalin, leu-enkephalin and β-endorphin). A large amount of work was carried out to demonstrate the actions and activity of these agents in a wide variety of test systems. The conclusion derived from such pharmacological studies was that these compounds in general had a spectrum of actions very similar to those of the plant alkaloid and synthetic opiates. Like morphine, the endogenous opiates were capable of producing analgesia,-tolerance and dependence, and positive reinforcement.

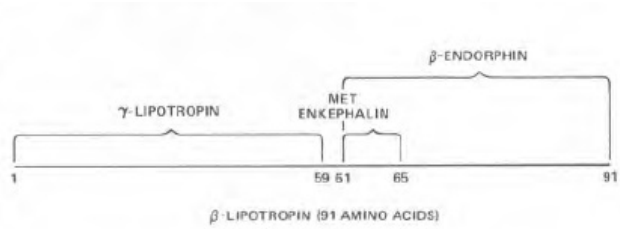

FIGURE 1-1.
Structure of β-lipotropin (β-LPH): Contains β-endorphin (β-END 61-91) and has the structure of methionine-enkephalin (61-65). β-LPH 1-59 is known as γ-LPH and is not opiate-like.

But, in early 1976, there developed a sudden embarrassment of riches in having three different opiate compounds. It was not clear at that point whether the shorter peptide (met-enkephalin) was a cleavage product of the longer peptide β-END and was therefore "simply" a metabolite of β-END, or whether β-END was "just" the precursor to enkephalin. The answer to that dilemma came fairly soon with the immunohistochemical work by several groups demonstrating that enkephalin and β-END had distinctly different distributions in the mammalian brain.' Both peptides occurred in cells, axons, and terminals, but the two systems exhibited no anatomical relationship to one another. In fact, it was soon concluded that enkephalin could be found in a large number of cell groups throughout the brain, from the spinal cord through the limbic system, whereas β-END had only one set of cells with very long fiber systems. Therefore, it appears that the enkephalins may have a local modulatory role because they are located in many different nuclei and are

associated with short fiber pathways and local circuit connections. In contrast, β-END is primarily associated with the limbic system; it arises from a single set of cells with a very widespread fiber distribution involving many limbic and brain stem structures. From a physiological point of view, the enkephalins might be thought of as being related to a wide variety of different functions. They are located so that they could be involved in pain perception, control of respiration, motor function, endocrine controls, and even affective states. On the other hand, β-END appears to be much more tightly related to upper brainstem and limbic systems and may be associated with system-wide changes.

Soon after the discovery of the enkephalins, it was possible to demonstrate several important characteristics of their action, suggesting their role as putative neurotransmitters. Not only were they stored intravesicularly with well-demonstrated interaction with specific binding sites, but they could also be shown to be released and degraded rapidly. Release studies were first carried out in humans, since enkephalin-like material could be detected in human lumbar fluid. The animal work on stimulation-produced analgesia had been extended to the clinical situation, and employed to relieve chronic intractable pain in humans. In neurosurgery, when these patients were electrically stimulated, the concentration of enkephalin-like material in the third ventricular fluid rose significantly. Finally, more recent evidence has suggested the presence of a specific, membrane bound enzyme, termed

enkephalinase, which degrades enkephalin with high affinity.

β-Endorphin/α-MSH Systems

Studies on the nature of brain β-END have proven to be considerably more complex and have raised more substantial questions than those associated with enkephalins. β-LPH was known as a β-MSH pituitary prohormone for several years prior to the discovery of the enkephalins and β-END. Immunohistochemical studies of β-LPH showed it in the pituitary, in the corticotrophs of the anterior lobe (cells that produce adrenocorticotropic hormone [ACTH]), and in all of the cells of the intermediate lobe. When β-END antisera became available, it was possible to demonstrate that β-END had precisely the same localization as did β-LPH, that is the corticotrophs of the anterior lobe and all intermediate lobe cells. Since ACTH was also present within these two cell types, there appeared to be an intimate association between β-END, β-LPH, and ACTH in the pituitary. Pelletier and coworkers and Weber and coworkers, using electron microscopic techniques, were able to demonstrate that β-LPH and ACTH immunoreactivity occurred within precisely the same granules in intermediate lobe and in corticotrophs. By demonstrating the presence of three substances in the same pituitary cells, that is, the corticotroph containing β-LPH, β-END, and ACTH, support was provided for the common biosynthetic origin of ACTH, β-END, and β-LPH. Mains and coworkers and Roberts and Herbert, using a mouse pituitary tumor

line, demonstrated that all three substances, ACTH, β-END, and β-LPH, were made from the same precursor molecule—the 31K dalton precursor, also known as pro-opiocortin (see figure 1-2). The 31K molecule contained the three structures mentioned previously, plus a new portion known as the 16K piece, which as yet has no clear physiology associated with it. An elegant and powerful extension of the investigation of this protein chemistry is the work of Nakanishi and associates, which demonstrates the DNA structure for the 31K precursor in the bovine pituitary. Work by Eipper and Mains and Gianoulakis and coworkers went one step further to show that the anterior lobe tended to cleave the 31K precursor down to $ACTH_{1-39}$ and β-LPH (with some β-END), whereas the intermediate lobe of the pituitary took the precursor one step further to produce β-END and y-LPH (and a small amount of β-LPH), and then cleaved ACTH into two fragments, an 18-39 piece known as corticotropin-like intermediate lobe peptide (CLIP) and a-MSH (N-acetyl $ACTH_{1-13}$ amide or a-Melanocyte Stimulating Hormone). Thus there were two biosynthetic endpoints of the pituitary 31K precursor. Naturally, immunohistochemical studies of the β-END/β-LPH cells in brain were extended to ACTH. Our own work and that of others demonstrated that the same cells in the brain that contained endorphin / lipotropin contained ACTH as well as the 16K piece. Thus, it appeared that at least three places in the central nervous system contained the genetic machinery for producing 31K precursor: two lobes of the pituitary and the brain arcuate nucleus (see figure

1-3).

As already mentioned, the two pituitary cell types tend to process 31K in different ways. The anterior lobe stops at an earlier cleavage point, mainly producing ACTH and β-LPH, the intermediate lobe progresses one step further in both cases reaching to *13-END* and a-MSH. The immunohistochemical studies of the brain that allegedly demonstrated "ACTH" in the brain were unclear. It was possible that the antisera employed were actually reacting with y-MSH and CLIP, rather than full ACTH. Further, there had been several studies demonstrating the presence of a-MSH peptide in the central nervous system and suggesting that this peptide had a distribution similar to β-END/β-LPH. In recent studies, we have been able to show that brain 31K cells resemble intermediate lobe cells in their biosynthesis, that is, they actually produce β-END and *a*-MSH in large proportions. In every case studied, each arcuate cell that produces β-END also produces a-MSH and vice versa. As an interesting aside, it should be noted that in the process of these studies a second a-MSH system was discovered in the hypothalamus, physically unrelated to the a-MSH /β-END system but positive for a-MSH using a wide variety of a-MSH antibodies. (We are once again reminded of the wisdom of nature in using active structures repeatedly: for example, the met-enkephalin structure occurs by itself and also in β-END.) Thus, it appears that a-MSH occurs as a neurally active substance, both as part of the 31K system and independent of it.

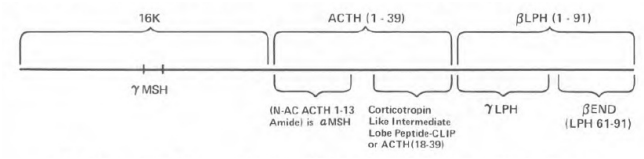

Figure 1-2.
The 31K precursor for ACTH, β-LPH, and β-END. See Figure 1-1 for β-LPH region model. ACTH 1-39 can be cleaved and modified to produce a-Melanocyte Stimulating Hormone (a-MSH) and Corticotropin-Like Intermediate Lobe Peptide (CLIP). The N Terminus of the 31K precursor is known as the "16K" piece and contains a potentially active sequence similar to ACTH/ a-MSH 4-10. This region is known as y-MSH. The anterior lobe of pituitary mainly produces ACTH 1_39> β-LPH, and some β-END. The intermediate lobe of pituitary and brain go further and produce β-END, y-LPH, a-MSH, and CLIP. The processing of 16K in these cells is currently under study.

Source: Mains, R.E., Eipper, B.A., and Ling, N. "Common Precursor to Corticotropins and Endorphins," *Proceedings of the National Academy of Science (U.S.A.),* 74 (1977). 3014-3018; and Eipper, B., and Mains, R. "Existence of a Common Precursor to ACTH and Endorphin in the Anterior and Intermediate Lobes of the Rat Pituitary," *Journal of Supramolecular Structure,* 8 (1978): 247-262.

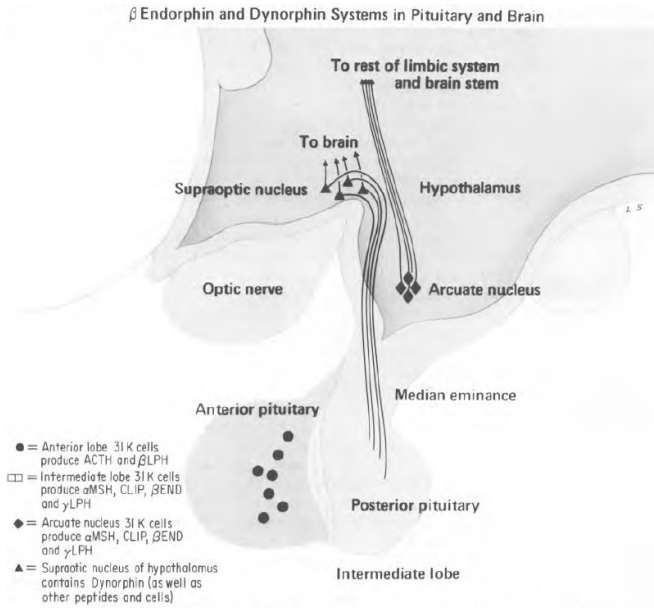

Figure 1-3.
Schematic of the pituitary and brain cell areas containing β-END and Dynorphin immunoreactivity. The anterior and intermediate lobe of pituitary and arcuate nucleus of hypothalamus contain the 31K precursor and products 08-END, β-LPH etc.—see legend). The supraoptic nucleus of hypothalamus contains Dynorphin cells which project to brain and to the posterior pituitary.

In further characterizing the β-END system in the brain, several kinds of studies have been carried out. For example, it has been demonstrated that β-END, when injected intra-cerebro-ventricularly, can produce analgesia and tolerance, as one might expect from an opiate. Yet, the effects are extremely long lasting, compared to those of enkephalin. The latter peptide is thought to be rapidly degraded—a characteristic of classical neurotransmitters.

Furthermore, β-END injections lead to a rigid "catatonic" state in rats, probably due to the production of limbic seizures. It has been shown that, when one looks at pituitary β-END and studies blood levels, severe stress to the rat can produce a substantial release of β-LPH/β-END in parallel with ACTH. Thus, at least the pituitary system is responsive to stress. It is known that β-END can be detected in the lumbar and third ventricular fluids of normal humans and in pain patients. It has been demonstrated (as mentioned for enkephalin) that when electrodes are placed in the thalamus of humans suffering from chronic pain, electrical stimulation produces pain relief for the patient and a substantial release of β-END immunoreactivity (more dramatic than was observed with enkephalin). In fact, it has been hypothesized that β-END is responsible for the prolonged period of analgesia associated with electrical stimulation. Finally, β-END in a highly specifically labeled form has been made available recently by Dr. C. H. Li,- and this material also has a high affinity binding site in the brain. We are able to conclude that β-END has many of the characteristics one would expect from an active neuronal substance: It is stored pre-synaptically, it is synthesized in the cell, it appears to be releasable by electrical and, most recently, by some hormonal means, it appears to produce substantial effects in its own right, and it possesses a binding site in the brain.

To add to the complexity of these systems, one should remember that not only do the β-END cells produce β-END but also produce ACTH in the

process of finally synthesizing a-MSH. Thus, a-MSH would appear to be a likely product for release. Not only is α-MSH synthesized in the brain, but it appears to be released into the cerebrospinal fluid (CSF) upon stimulation. In recent studies, the authors and others have been able to demonstrate the presence of a-MSH immunoreactivity in lumbar fluids and its release into ventricular fluids of patients being stimulated for pain relief. The problem of establishing the presence of a receptor for α-MSH and/or ACTH in the central nervous system is a long and complicated one. The fairest summary is to state that many laboratories have tried. Most recently, our laboratory has been successful in producing a small amount of ACTH and a-MSH binding in the brains of several mammalian species, tending to indicate there are relatively few receptor sites available for this material, in contrast to β-END. Further, in very recent studies it has been possible to demonstrate that α-MSH and its de-acetylated form are both active in the brain when microinjected into the midbrain periaqueductal gray. It appears that a-MSH is a reasonable candidate for a neurally active substance in that it possesses a binding site, exhibits behavioral effects, and appears to be releasable. However, the reader should be cautioned that these data are preliminary and need further support.

The general principle that a single neuron tends to produce a single active substance has now been brought into question, not only by the work reviewed here but by the elegant work of Hokfelt over several systems, peripherally and centrally. In considering the problem of multiple substances

being produced and very likely released by a single neuron, a huge set of complex issues arise. For example, how does the synthesizing neuron control the activity of two potentially active substances? Are there two receptor sites post-synaptically? How do they feed back on the synthesizing neuron? Are they both always released in a fixed ratio? Or does the synthesizing neuron have the capacity to preferentially inhibit one and release the other, or can the neuron make one form relatively more active than the other?

Another issue very relevant to clinical studies is that of the proper way to mimic normal physiology. When one administers an opiate agonist by itself, it is clear that that drug is not mimicking the endogenous β-END/α-MSH system's normal action. It is very likely that the endogenous system is exposed to β-END and α-MSH simultaneously—two different substances for two different receptors. It might be suggested that the proper way to approach such clinical studies would be to administer α-MSH or β-END agonists or antagonists together in some controlled fashion, rather than attempting to separate them, as many studies have inadvertently done.

Dynorphin

Most recently, a new opiate peptide has been discovered by Goldstein and his coworkers at Stanford University. They have called this new peptide dynorphin (from *dynis,* "powerful"). Dynorphin includes the full structure of

leu-enkephalin as its first five residues, followed by a highly basic region. This material is extremely potent in the guinea pig ileum; it has yet to be thoroughly studied in the brain. Immunohistochemical studies have revealed that it occurs in the posterior pituitary almost exclusively (unlike β-END which occurs in the intermediate lobe and anterior pituitary). It also has a distribution in the brain with cells in the supraoptic nucleus and perhaps elsewhere and fibers throughout limbic and brain structures. Some fibers have been detected in the guinea pig ileum. While little is known about this newly discovered endorphin, it is clear that its distribution in the brain is different from β-END; its relationship to the enkephalin system is unclear. The cellular overlap relationship between dynorphin and the other posterior lobe peptides (oxytocin and vasopressin) is currently being studied. Certainly, questions of circulating blood levels, CSF levels, or relationship to addiction or psychosis are yet to be addressed, and should prove of great interest.

Summary

In studying the role of endorphins in psychosis, we are faced with three major neuronal systems in the brain, intimately associated with the pain, affect, and endocrine systems. These opiate peptide systems are enormously complex in their own right, and at least one of them appears to contain one other active substance (β-END/α-MSH). Another appears either to occur in the same cells (met- and leu-enkephalin) or to have two different systems, but

of extremely similar distribution. The last one, dynorphin, has a third set of brain fibers and major endocrine ramification. By demonstrating the presence of so many systems, all of which would appear to have their own opiate receptors, we are faced with enormous complexity associated with those receptor measurements. It does not seem unlikely that each of these neuronal systems should have a relatively different receptor subtype in order to account for the differences in peptide structure. Of course, the neural connectivity of these systems leads to quite different physiological ramifications.

While this review has focused on the brain and pituitary, it should be noted that opiate peptides exist in the peripheral nervous system—for example, in the gut adrenal. These peripheral systems present their own fascinating complexities. For instance, it has recently been discovered that enkephalin and some larger enkephalin-containing peptides occur within the adrenal medulla, are stored within norepinephrine and epinephrine-containing granules, and may be co-released when those catecholamines are released.

Endorphins are candidates for brain neurotransmitters or neuromodulators, but they are also pituitary, gut, and adrenal hormones. Their peripheral targets are yet to be determined, and their primary brain functions yet to be defined. In retrospect, opiates such as morphine are

understandably potent since they access receptors in the brain and in the periphery for numerous endogenous systems with multiple roles. While the complexity of endorphins indicates their importance in behavior, it creates several logistics problems for the clinician. With pharmacological tools, it is difficult to influence one system without affecting the others. Enkephalin analogues are likely to be recognized at the brain or peripheral sites that normally only interact with β-END, and vice versa. Antagonists will block endogenous opiate effects indiscriminately, though possibly with differential efficacy. Thus, interpretation of behavioral and clinical data should proceed cautiously.

Clinical Studies

In the following section we summarize the several investigations of psychosis that have been carried out using opiate pharmacology (or the opiate peptides). In many ways, it is too early to draw conclusions of a valid or lasting nature from this very preliminary set of investigations. Nonetheless, the results to date will probably help shape future research, focusing it in specific directions, while eliminating simplistic approaches or invalid hypotheses.

In general, there have been five main approaches to the problems of relating endorphins to psychiatric illness. These five include studies of

cerebrospinal fluid chemistry, the actions of opiate antagonists on psychiatric symptomatology, the actions of opiate agonists (including β-endorphin on psychiatric symptomatology), the attempted removal of endorphins by hemodialysis, and finally, the administration of opiate inactive structural variants of β-END (des-tyrosine-y-endorphin) to schizophrenic patients. The general thrust in each of these areas has either been aimed at altering symptoms of specific psychiatric illnesses or at correlating the occurrence of the state of the illness with the level of endorphins in CSF, blood, or dialysate.

Cerebrospinal Fluid Studies

Soon after the discoveries of the endogenous opiate peptides, Terenius and associates and Lindstrom and associates carried out a series of clinical studies evaluating the endogenous opiate peptide levels in schizophrenic and manic patients. These investigators did not identify the structure of the peptides they were studying, but only characterized them in terms of their column chromatographic behavior and interactions with opiate receptors. In Terenius' nomenclature, Fraction 1 is a higher molecular weight fraction, but does not appear to contain β-END, whereas Fraction 2 is a lighter fraction and does appear to contain enkephalin-like peptides. When untreated schizophrenics were evaluated, they were found to have elevated levels of Fraction 1 in six out of nine cases; but after treatment, levels returned to normal (less than 2 pmoles per ml) in seven of nine cases. Fraction 1 was

further elevated in three out of four cases of mania. However, these same manic subjects also demonstrated highly elevated levels of Fraction 2 during normal mood states. Even though Fraction 1 and Fraction 2 have not been specifically identified, there appears to be significant indication that these opiate peptide fractions may reflect either the effect of treatment, or some aspect of underlying psychopathology in schizophrenic and manic patients. In a replication and extension of this work, Rimon and colleagues have confirmed the elevation of Fraction 1 in first break acute schizophrenics and a few reentering schizophrenics with some normalization after treatment. No pattern to Fraction 2 was detected. Recently, Domschke and colleagues have described studies of spinal fluid β-END in normal and neurological controls and in acute and chronic schizophrenics. They conclude that normal subjects have values of 72 fmoles per ml, whereas neurological controls have values of 92 fmoles per ml. The chronic schizophrenics had only half the normal values (35 fmoles per ml) and acute schizophrenics (definition unclear) had values of 760 fmoles per ml. These normal and neurological control values are in general agreement with the study of Jeffcoate and associates of normal CSF, in which β-END and β-LPH were found in a 60-80 fmoles per ml range. However, both these studies are in striking contrast to the studies from several other laboratories in which the levels of β-END and β-LPH have been found to be much lower. Studies by Akil and colleagues, and Emrich and colleagues generally find normal CSF values to be much lower, in the range of 3-12

fmoles per ml for β-END. Akil and colleagues have studied over sixty spinal taps from chronic schizophrenics and normals and found no difference between them. In a study by Emrich and coworkers, normals and groups of patients with meningitis, disk herniation, lumbago, and schizophrenia all show approximately the same level of CSF endorphins (in the 10-15 fmoles range). Thus, there appears to be substantial disagreement, not only on the levels seen in schizophrenia, but also on the levels seen in normal individuals as well. The studies reporting lower concentrations have used more elaborate biochemical controls and more accurate calibrations of antisera and extraction procedures.

Finally, Dupont and coworkers, in a very interesting study, have approached the problem of peptidase activity in the cerebrospinal fluid of schizophrenics and normals and find that peptidases which are capable of degrading enkephalin are much more active in the spinal fluid of schizophrenics than in that of normal individuals. However, in an attempt at replication, Burbach and associates were unable to reproduce the finding of increased activity of an enkephalin-degrading enzyme when CSF of schizophrenics was contrasted with controls. They were further unable to demonstrate altered /8-END breakdown in the same subjects. Thus, the question of altered metabolism of these opiate peptides in the CSF of schizophrenics remains open.

In summary then, investigation of CSF chemistry of the opiate peptides is technically difficult and at an early stage. Studies by Terenius and coworkers would appear to be most interesting, as they show consistent pre- and posttreatment differences. The work of other investigators in terms of levels of β-END tends to be inconsistent and falls into two disparate groups.

Opiate Antagonists

Following up on the original results of their studies of elevated endorphin levels in CSF, Gunne, Linstrom, and Terenius attempted to reverse some of the symptoms of schizophrenia by administering the opiate antagonist naloxone. Generally, they reasoned that since elevated levels of endorphins occur during the acute phase of an illness, and decreased levels of endorphins during the recovery phase, it might be concluded that the endorphins were in part responsible for the worsening of psychosis. They speculated that the use of the opiate antagonist naloxone might produce a change in psychotic symptomatology. The initial study of Gunne, Lindstrom, and Terenius was a single-blind study in which a modest dose of naloxone (0.4 mg) was given to six schizophrenic patients. Four of these patients reported significantly decreased auditory hallucinations. This study resulted in several attempts at replications using a double-blind crossover design with basically negative results. Volavka and coworkers used the same dose of naloxone on seven well-chosen schizophrenic subjects and observed no effect.

This was a careful study which followed the effects of intravenous administration for over twenty-four hours. Janowsky and coworkers used 1.2 mg of naloxone in studying a rather heterogeneous group of patients for only one hour; they also detected no effect on their eight subjects. Kurland and associates used between 0.4 and 1.2 mg naloxone and found no statistically significant effect on their eight patients. Dysken and Davis, in a single-blind study, evaluated the effects of 20 mg naloxone for only a ten-minute period in a single subject to no avail. Lipinski and associates, in a double-blind crossover, gave 1.6 mg naloxone to schizophrenic patients with no observed effect. Finally, Davis and associates, in a double-blind crossover design, generally using low doses (0.4 mg and in a few instances using 10 mg naloxone), studied fourteen schizophrenic patients, and found a change in "unusual thought content" on the Brief Psychiatric Rating Scale. These same investigators found no change in their "affective" patients. Thus, from the original six studies, only Davis and associates supplied any support for the observations of Gunne and coworkers. However, it should be noted that these were basically low-dose studies using 1.2 mg of naloxone or lower doses.

From basic pharmacological work with the opiate peptides across several test systems, it had become clear that the opiate peptides were relatively resistant to the effects of naloxone, often requiring higher doses, and that naloxone itself, although short-lived in its reversal of morphine, could be detected in its effects on endorphin systems for several hours.

Therefore, it seemed logical to attempt to study the effects of naloxone on schizophrenia, using much higher doses and following the patients for longer periods of time. In a study reported by this group, a large number of schizophrenic subjects were prescreened. The authors were able to find patients who met the Research Diagnostic Criteria (RDC) for schizophrenia, were diagnosed either as chronic undifferentiated or paranoid, and were at the same time cooperative, stable on their medication, and noted for their chronic (twice per hour) pattern of hallucinations. In this double-blind crossover design, 10 mg of naloxone was used and the patients were followed for up to two days after the infusion. Under these conditions, naloxone was found to produce a statistically significant effect in reducing the number of hallucinations in these chronic hallucinating schizophrenics at one and one-half to two hours after infusion. Six of the nine patients subjectively reported a clear decrease in auditory hallucinations. It must, of course, be admitted that this is a highly selected subgroup, as over 1,000 schizophrenic patients at the Palo Alto Veteran's Hospital were screened for this study.

Emrich and coworkers''' report two studies in which they evaluated the effects of naloxone on schizophrenics and other psychotic patients. Their general impression in one study was that naloxone was effective in reducing schizophrenic hallucinations, using between 1.2 and 4 mg of naloxone, at time points between two and seven hours after infusion. In their next study, using much larger doses of naloxone (24.8 mg), although there was a reduction in

psychotic symptoms, no reduction in hallucinations were reported in twenty subjects tested. Davis and coworkers in a second double-blind study, using 15 mg of naloxone, found that there was a significant reduction in unusual thought content in their schizophrenic patients and this effect tended to be most pronounced in patients who were maintained on neuroleptics but had been somewhat resistant to their effects. Finally, Lehmann and associates in single- and double-blind paradigms, using 10 mg of naloxone and following the patients for up to three hours, found that three of the six patients reported reduced "tension" and five of five patients demonstrated lessening of their symptoms of thought disturbance and hallucinations.

Thus, when one examines high-dose (between 4 and 25 mg), double-blind, crossover naloxone studies in schizophrenic patients, the results are consistently positive, if somewhat variable. These studies variously report changes in auditory hallucinations, psychotic symptoms, unusual thought content, or tension. From a clinical point of view, all of these symptoms would appear to be essential to the process of psychosis, but their common vulnerability to naloxone is somewhat disconcerting to the clinical investigator, as they are not normally thought of as involving the same underlying variable. Thus, some question should be raised about the nature of the measurement instruments and the consistency of the effects of naloxone. It is of considerable interest, however, that all of the five studies using high-dose naloxone were positive, whereas the majority of the studies using low-

dose naloxone were negative. It is of further interest that the effects reported in the high-dose naloxone studies have generally occurred much later than one would expect from the classical pharmacology of that opiate antagonist. This raises an important theoretical question: Is the naloxone effect due to opiate receptor blockade, or is it the result of secondary or tertiary effects resulting from that blockade?

Finally, there has been one study of the effects of naloxone in mania. The study used 20 mg naloxone and reported a reduction of irritability, anger, tension, and hostility in four out of eight manic patients.

The opiate antagonist naltrexone would appear to have several advantages for the study of the effects of antagonists in schizophrenia. It can be given in rather large doses, in an oral form, and has a very long period of action. However, there have been few attempts to study naltrexone in schizophrenia. Milke and Gallant, in an open-label design, gave 250 mg of naltrexone to three schizophrenic patients, but observed no effect. Simpson, Branchly, and Lee" studied the use of up to 800 mg naltrexone in a single-blind study of four patients and found no effect.

The authors have evaluated naltrexone in a single-blind paradigm (two subjects) and a double-blind paradigm (two subjects) and found a confusingly mixed picture. Single-blind subjects were improved on 250 mg naltrexone. Of

two double-blind subjects, one improved at between 250 and 400 mg, and one worsened, and one subject (one of the single-blind subjects) worsened on 800 mg. The effects of naltrexone would therefore appear to be poorly studied, but also generally negative, although it must be admitted there is the possibility of a therapeutic window in the 250 to 400 mg range.

In an elegant, if indirect, series of studies, Davis and coworkers have been able to show a defect in pain response (flattened evoked response) in their schizophrenic patients. This pattern is similar to that seen in normal patients on morphine. When several schizophrenic subjects were given naltrexone, their evoked responses changed so that they were much more "normal" in appearance. This, again, is suggestive of over-activity in endogenous opioids in some schizophrenics. A broader and more extensive set of studies is needed, however. As Davis and coworkers point out, this paradigm might be useful for selecting individuals with endorphin related psychoses.

The general impression emanating from the study of opiate antagonists in schizophrenia is one of a rather delicate, ephemeral effect with some inconsistency. Certainly, low doses of naloxone can fairly be said to be ineffective in schizophrenia. A large number of excellent and well-qualified laboratories have evaluated its effects and agree on either negative or transient effects. Higher dose naloxone studies are consistent in that there

appears to be some effect in each study. However, the nature of that effect tends to change between measurement scales and research groups. Naltrexone does not appear to be particularly effective, although it has not been carefully evaluated.

β-Endorphin Injections

Kline and coworkers originally reported that between 1 and 9 mg of synthetic β-END, when injected intravenously (IV) in an open-label or single-blind fashion, was very effective in altering a wide variety of psychiatric symptoms in schizophrenia and depression. This study was, of course, complicated and difficult to assess in that the patients were well known to the senior investigator, a small amount of β-END was given, and the design was not double-blind. Since the number of subjects carrying the same diagnosis was limited, different drug doses and testing conditions were used. It was not possible to carry out a rigorous statistical analysis of this data. Angst reported that three of six depressed subjects became hypomanic after infusion of 10 mg β-END IV. More recently, the authors have studied the effects of 20 mg of β-END IV in a double-blind crossover design with ten schizophrenic subjects and found a very modest improvement that was not detectable clinically but was seen in the rating scales on days three and five following the infusion. This effect is a very mild one and is smaller than that associated with the first week of the study (an “adaptation” period that was not included in the data

analysis). Several technical controls were run to ensure the proper administration of a biologically active compound of the proper specificity. Plasma kinetics by radio immuno assay (RIA) (associated with a rapid rate of infusion and pre-coating of the syringes and tubing), evaluation of serum prolactin responses, and, in one case, cortical EEG responses were all evaluated and found to be consistent with the injection of an active opiate-like material with the proper molecular weight. Catlin and coworkers have reported, in a very similar design, that β-END is either not effective or mildly agitating to their schizophrenic subjects on the day of infusion. They have also evaluated the compound in depression and found it to be moderately and transiently effective. Finally, Bunney and coworkers have been working with IV *13-END* in schizophrenic patients and, to date, have seen no reliable effects.

An enkephalin analog FK33-824 synthesized by Sandos has been used by two groups in studies of schizophrenia. Nedopil and Ruther have reported in an open-pilot study that nine schizophrenic patients (receiving 0.5 mg and 1 mg per day for two days) improved significantly. The improvement was reported to last for one to seven days. Another group, Jorgensen and associates, also treated nine chronic psychotic patients in a single-blind fashion and reported striking lessening of their subjects' hallucinations.

The general impression of β-END injections as a mode of treatment for schizophrenia is that of very modest or nonexistent effect. It must be pointed

out that a single injection of a neuroleptic would probably be equally ineffective under similar circumstances, especially if the effective dose was not known. Several of the aforementioned studies of β-END or the FK33-824''' were either single-blind or open-label and therefore susceptible to the criticism of suggestion, subject set, and expectancy by the patient. Other technical problems associated with β-END are rather severe. It is unclear whether β-END is transported into the central nervous system. Recent data suggest that a modest amount is. However, it is not known whether there is substantial breakdown under these conditions or whether the β-END can in fact easily reach the most effective sites. Nor is it clear whether β-END should necessarily be more effective than a synthetic alkaloid such as morphine or levorphanol, unless one invokes notions of multiple opiate receptors, whose relation to endogenous opioids has yet to be elucidated.

Hemodialysis and Leu-5-β-END

In 1977 Wagemaker and Cade reported that by dialyzing schizophrenic subjects on a weekly basis it was possible to produce a substantial and positive shift in their level of psychopathology. Simultaneously, they and their colleagues reported the existence of a peptide not previously described—that is, a leucine-5-β-END. The existence of leucine in position 5 of β-END had not been reported in any tissue of any species prior to this announcement. They further argued that the effectiveness of dialysis depended on their ability to

remove leucine-5-β-END and thereby reduce the amount of this “aberrant” endorphin from the plasma. The hypothesis was that this was an unusual material and that it was producing an unusual effect (that is, psychosis). Thus, several issues were brought together in one very complex package: the question of the clinical efficacy of dialysis, the question of the existence of leucine-5-β-END, and the question of whether removal of that compound or any endorphin by dialysis was an effective means of treating schizophrenia. To address the first issue, there are ongoing studies in several centers using hemodialysis or pressure dialysis. One study by Emrich and associates of three patients reports no benefit from hemodialysis. To date, no other results have been published. There have been many presentations, discussions, and case histories in which most patients are not responsive and some anecdotal reports in which an occasional patient is responsive to dialysis. The type of dialysis membrane, the psychological nature of the setting, and the actual diagnosis of the patient are all major issues. Unfortunately, no conclusion can be reached on the clinical efficacy of hemodialysis as the studies have not been completed. In addition to these preliminary reports, Port and associates have carried out a literature retrospective study of fifty schizophrenics in the Veterans’ Administration system who were dialyzed for renal problems. They found that over the time of the dialysis, forty patients were unchanged, eight were improved. They argued that from the multiphasic character of schizophrenia and the heterogeneity of symptoms one would expect this

degree of fluctuation among fifty patients. The investigators also contended that the kidney is much more efficient at filtering these molecules from the plasma than is the dialysis machine, and, therefore, they questioned the effectiveness of dialysis as a means of removing from plasma molecules the size of β-END or leucine-endorphin.

On the chemical side, Lewis and coworkers studied the hemofiltrate from dialyzed schizophrenics and could detect no met-5-or leu-5-β-END in the hemofiltrate. It should be pointed out that the level of sensitivity for detecting the levels of met-endorphin (β-END) in normal individuals was quite low in this study. However, the levels reported by Palmour and coworkers are 1,000- to 10,000-fold higher than in normal individuals and should have been detected using the techniques of Lewis and associates.

Ross, Berger, and Goldstein addressed the problem at a somewhat different level. They argued that if schizophrenics had extremely high levels of β-END or leucine endorphin, then this amount of peptide should be obvious in the plasma of these subjects (in contrast to normal individuals) using radio-immunoassays for both met and leu-endorphin. In ninety-eight patients and forty-two normals, they found an amazingly similar set of levels for endorphin-like immunoreactivity (schizophrenics averaged 2.8 fmoles per ml; normals, 2.4 fmoles per ml). Further, they were unable to detect leu-5-β-END in the dialysate from several schizophrenic patients.

The argument for the existence of a leucine-5-endorphin or elevated levels of endorphins in schizophrenia currently appears to be difficult to justify. Although there have not been a large number of studies, the results of the studies that have been carried out are clear. It is tempting to speculate that because there do not appear to be aberrations of endorphins in schizophrenia, dialysis should not be effective. However, the most productive course, in the long run, would appear to be to wait until the clinical studies are completed and then to address the issue of the mechanism of action of any positive result.

Des-Tyr[1]-Gamma-Endorphin (β-LPH 62-77)

For several years, in a series of pioneering investigations, De Wied and coworkers have been studying the behavioral effects of a large number of neuropeptides. More recently, they have studied the effects of smaller structural variants of β-END, known as a-END and y-END, and have found that y-END had effects similar to those of haloperidol, whereas a-END acted more like an amphetamine. This rather extensive set of behavioral and structure activity studies has been most impressive in that they have been confirmed generally by other groups. It has also been possible to alter the molecules so that their basic haloperidol or amphetamine-like effects are still present, but are no longer active in opiate systems (that is, the initial tyrosine from γ-END is removed, resulting in des-tyrosine-γ-endorphin [DTγE]). Following the

animal behavioral experiments with y-END and DTγE, De Wied and coworkers proceeded to test DTγE for its haloperidol-like effects in psychiatric patients. Thus, Verhoeven and coworkers ran a single-blind crossover study, using DTγE in daily x mg intramuscular (IM) injections. They reported rapid temporary improvement in schizophrenic symptoms in six out of six patients, with a persistence of that improvement in three of the six patients (all six patients were drug free). They then carried out a double-blind crossover study, using the same compound in the same format. Again, they report substantial improvement in a broad range of schizophrenic symptoms in eight subjects. Several clinical studies by other groups are underway.

There have been studies attempting to investigate whether DTγE acts at the opiate receptor or at the dopamine receptor. Binding in tissue homogenate has not shown any action of this compound at either receptor. However, Pedigo and coworkers have shown that when the compound is administered *in vivo* to rats it decreases the amount of spiroperidol that can bind to the dopamine receptor. Thus, it is conceivable that it has an effect in the live animal that is not seen in *in vitro* assays.

The mode of action of this agent is not clear. Perhaps it acts through the subtle alteration of the dopamine binding previously described. Or perhaps it is an effect on the intermediate metabolism of β-END, acting via negative feedback to alter the amount of neuroactive substance the cell produces. In

support of this hypothesis, Burbach and coworkers have reported the existence of DTγE, γ-END, α-END, and DTαE in human lumbar CSF and the formation of α-END, γ-END, DTαE, and DTγE from β-END in brain synaptosomal preparations. Finally, there may be a primary action of the compound on its own receptor in the brain. As yet, none of these possible modes of action has been verified. Certainly, if the agent is demonstrated to be effective in other clinical studies (several studies- are currently in the planning stages) then a new approach to the pharmacology of schizophrenia will have been opened. To date, it is reported to be capable of producing antipsychotic effects with no major problems associated with its administration. On a more theoretical level, there are exciting issues associated with the agent in that it might allow a conceptualization of the neuronal chemistry of the psychoses which goes beyond the dopamine theory and the use of anti-dopaminergic agents.

General Summary

It appears that the CSF studies are promising if somewhat vague and confusing in that there are some endorphin fractions (uncharacterized as yet) that would appear to be very sensitive to the psychotic state of certain individuals. The opiate antagonist naloxone has proven effective in schizophrenia and mania at high doses but not at low doses. Unfortunately, these are rather fleeting effects, difficult to measure, and varying from

investigator to investigator. The infusion of β-END itself has been extremely difficult and costly to evaluate. It would appear that a single infusion of β-END is minimally effective as an antipsychotic when administered by some investigators and mildly agitating to the patient when administered by another. In some manic-depressive patients, β-END seems to produce a switch from depression to hypomania. It is reported by some investigators to be an effective antidepressant (if somewhat transient and expensive). The enkephalin analog FK33-824, according to two open- or single-blind reports, seems to be of promise as an antischizophrenic agent. Hemodialysis in schizophrenia is even more complicated, some groups finding it to be effective, others not. The completion of these studies will require some time. However, it seems at this writing that the existence of a leucine-5-β-END is unlikely. Finally, destyrosine-γ-endorphin has been studied fairly extensively in animals, but only in a limited fashion in humans. It does, however, appear to hold great clinical and theoretical promise, should its efficacy be borne out by future studies.

In considering the possibility of an integrated endorphin theory of schizophrenia, which would help make understandable the modes of action of these compounds and their relationship to psychopathology, one is struck with the apparent contradictions of the clinical data and the tremendous diversity of basic information. While it may be possible to construct a hypothesis that integrates the apparent contradictions, the wisest course

seems to be to wait until clearer basic science patterns are available and until the various clinical areas are clarified. At that point it may be possible to attain a comprehensive overview that takes into account the basic biology and the psychopathology.

As for the study of affective diseases and endorphins, there are even fewer data. Depression has not been studied with respect to CSF levels of the endorphins, nor have the antagonists been studied for their effects on depression. β-END itself is reported to be moderately effective against depression, but it is not clear that β-END effects in depression surpass those of morphine. There have been no studies with the enkephalin analog, dialysis, or DTγE in depression. In mania, there is preliminary evidence for elevated CSF endorphins (type uncharacterized), and in a single study some effects of opiate antagonists on manic symptoms have been shown. However, there are no other reported studies as of this writing. Therefore, the affective psychoses, which in some ways would appear to be an extremely logical area for study of the effects of opiate agents, have been very poorly examined. One might anticipate a rich reward from careful study of endogenous depression, the endocrinology associated with the effects of opiates, and the mood-altering properties associated with the various types of opiate compounds.

Perspectives and Problems

Some of the issues associated with the study of endorphins and psychosis may be thought of as being related to a lack of precise tools. Certainly, the chronic and persistent complaint that clinical diagnoses are variable and at times unreliable should be borne in mind. But one cannot blame the entire problem in clinical studies on the unreliability of psychiatric diagnoses. The lack of proper design in the use of open-label or single-blind studies has caused problems. Furthermore, the specificity of the pharmacologic agents used, their routes of administration, and the nature of the brain structures affected are open to question. For example, naloxone is not a specific antagonist for enkephalin. It would appear to be active against β-END and dynorphin, as well. We have no specific antagonists aimed at the hypothesized multiple types of opiate receptors. There is a great need for increasing the specificity of opiate agonists and antagonists. These agents should be targeted against specific receptor types in order to alter the physiology of particular systems. For example, it would be most useful to have a specific β-END-like agonist known to cross the blood-brain barrier, so that one could mimic the effects of β-END. However, at the same time one would need a similar compound to mimic the effects of α-MSH, for, as mentioned previously, both β-END and a-MSH are contained within the same neurons and would appear to be co-released when the neurons fire. Therefore, in order to mimic the normal physiology of that system, it would be necessary to produce actions at the appropriate receptors by using both endorphin and a-

MSH analogues. Thus, the pharmacological requirements for improved psychiatric studies are indeed considerable.

In writing this chapter, two different thoughts have come to mind. One is that this is a difficult chapter to write at this juncture. The careful reader has undoubtedly realized by this point that, in many ways, this is a highly premature piece of work. To date, there is no great consistency in the role of endorphins in psychosis. There are trails; there are hints; there is confusion. There may even be some pleasant surprises in the literature, but there certainly emerges no compelling hypothesis. Even tentative conclusions are likely to prove naive and incomplete. The other thought that comes to mind is that this is, in several ways, a rather narrow chapter. It does not take into account an enormous set of recently described substances in the central nervous system. Many of them are peptides and appear to be well located for effects on the limbic system. They represent likely candidates for actions of interest to the psychiatrist. For example, arginine vasopressin has been implicated in memory, opiate addiction, stress, and affect. Cholecystokinin, an active peptide in the brain, has recently been associated with the dopaminergic system, thereby implicating it in many actions classically associated with dopamine. These are but a few of a much larger set of substances, which includes neurotensin, somatostatin, bradykinin, and Substance P. It is clear that the neuropeptides and other neuromodulators, such as the endogenous ligand for diazepam (Valium), are going to mean a

very major shift in the role of brain biology for the psychiatrist's understanding of the nature of psychological processes in general and the psychoses in particular.

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Notes

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