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Endorphins, Dopamine, and Schizophrenia*

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Abstract

The theory that alterations of dopaminergic synaptic transmission may play a role in the pathogenesis of schizophrenia is widely accepted. A more recent theory links the endorphin system to the etiology of schizophrenia. We propose that these two theories may be combined into a single model. Recent neurochemical and pharmacological findings have indicated close functional relationships between the endorphin and dopamine systems. Endorphins modulate dopaminergic synaptic transmission by exerting both presynaptic and postsynaptic effects. On the molecular level, this modulation may involve the activity of nucleotide cyclases and protein phosphorylation systems. Thus, the dopaminergic neuronal hyperactivity, currently believed to be related to schizophrenia, may be caused by a primary alteration in the endorphin system. Several hypotheses about the nature of that alteration have been advanced and tested in therapeutic experiments with schizophrenic patients. These experiments have not yet yielded definitive results.

Endorphins ("endogenous morphines") have become one of the most popular research topics in behavioral sciences, pharmacology, neurochemistry, and a number of other fields. Reviews of the neurochemistry and pharmacology of opiate receptors and endorphins are available elsewhere (e.g., Snyder 1978). We have recently reviewed the implications of the endorphin research for psychiatry (Verebey, Volavka, and Clouet 1978). The purpose of this article is to focus on the implications for schizophrenia and to relate the dopamine hypothesis of schizophrenia to the more recent biochemical and pharmacological findings on the role of endorphins, cyclic nucleotides, and protein phosphorylation in the regulation of neuronal function. The presumed relationships are summarized in figure 1.

Dopamine Hypothesis of Schizophrenia

Much research on the role of dopamine in schizophrenia has been done; a recent review provides a critical summary (Carlsson 1978). Briefly, the dopamine hypothesis suggests that in schizophrenia the brain cells that use dopamine as a neurotransmitter are hyperactive. This hypothesis has been formulated within the framework of the classical description of neuronal transmission: A neurotransmitter is synthesized and released from the presynaptic cell to impinge on specific postsynaptic receptors, resulting in a continuity of neuronal information transfer. The hypothesis derives its primary support from pharmacological and therapeutic studies. The most effective drugs (neuroleptics) in the treatment of schizophrenia have been found to be powerful blockers (antagonists) of the cellular receptors for dopamine (Snyder 1976). Moreover, the clinical efficacy of different neuroleptics parallels their competitive ability in binding to these receptors (Creese, Burt, and Snyder 1976). Additional support is derived from the observation that the antipsychotic effects of the neuroleptic drugs are potentiated by alpha-methyl-para-tyrosine (Walinder et al. 1976), an inhibitor of a key enzyme (tyrosine hydroxylase) in the biosynthesis of dopamine. These re-

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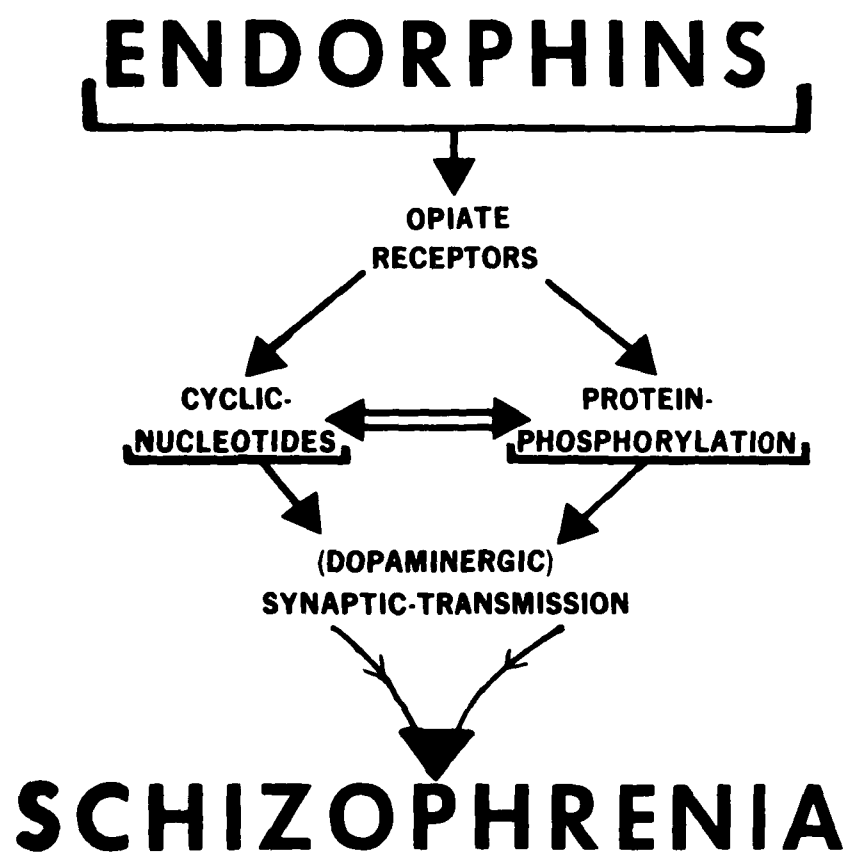
Figure 1. Interactions of endorphins, cyclic nucleotides, and phosphoproteins in neuronal processes related to schizophrenia



ports indicate that the dopamine system needs to be suppressed for successful treatment of schizophrenic patients. Other support is provided by studies in which the dopamine system is activated—for example, by amphetamines—which results in an increase of psychotic symptoms (Angrist and Gershon 1970). As impressive as the above observations are in their support of a hyperactive dopamine system in schizophrenia, the fact is that not all patients respond positively to neuroleptic treatment. Moreover, no direct evidence for the dopamine hypothesis has been obtained by characterizing the composition of body fluids or postmortem brains of schizophrenics. The chemical investigation of dopamine and its metabolites in urine, blood, and particularly cerebrospinal fluid has provided meager support at best for an increased dopamine activity in schizophrenics (Bowers 1974; Farley, Price, and Hornykiewicz 1977; Post et al. 1975). Recent evidence (Lee et al. 1978) indicates that dopamine receptors are indeed increased in the brain of schizophrenics, but that might be an effect of neuroleptic treatment rather than an intrinsic feature of schizophrenia.

More recent findings on the regulation and modulation of synaptic neurotransmission have resulted in clinically important extensions of this classical system. Two recent clinical reports exemplify the application of the increased understanding of basic synaptic function to patient treatment. Apomorphine, like dopamine, is reportedly a stimulator (agonist) of the dopamine postsynaptic receptors (Anden et al. 1967; Ernst 1967), and thus should be expected to worsen psychotic symptoms (Yaryura-Tobias, Diamond, and Merlis 1970). At lower concentrations, however, apomorphine apparently acts selectively on presynaptic dopamine receptors, which then inhibit dopamine release (Kehr et al. 1972; Nagy et al. 1978). These presynaptic receptors are involved in monitoring the amount of dopamine so as to prevent further transmitter release. Using this information about the possible dual action of apomorphine, Smith, Tamminga, and Davis (1977) and Tamminga et al. (1978) treated a small group of schizophrenics with low doses of apomorphine. These patients showed clinical improvement. The authors attributed the effectiveness of apomorphine to the suppression of dopamine action through these presynaptic mechanisms. In a different approach, Alpert and Friedhoff (1976) have treated tardive dyskinesia patients with incremental doses of L-dopa, a precursor of dopamine. The dyskinesia got worse, presumably because more dopamine was made. However, following *abrupt* discontinuation of L-dopa, the dyskinesia markedly improved, indicating the possibility of receptor modification (Friedhoff 1977).

Biochemistry of Dopaminergic Transmission

In the preceding section, we have presented evidence indicating that alterations in dopaminergic synaptic transmission may account, at least in part, for some of the symptoms of schizophrenia. An understanding of the molecular mechanisms that play a role in this transmission process may shed light on molecular events possibly involved in bringing about schizophrenic symptoms. We shall therefore briefly present here some aspects of the biochemistry of dopaminergic synaptic transmission, with special emphasis on recent findings implicating cyclic adenosine 3',5'-monophosphate (AMP) and specific phosphoproteins in this process. The efficacy of the transmission process depends on two main events: first, the metabolism of dopamine and its release into the synaptic cleft, and second, the consequences of the interaction of dopamine with its postsynaptic receptors. The information provided by the neurotransmitter-receptor interaction is conveyed into the cell by "second messengers." Kebabian, Petzold, and Greengard (1972) have demonstrated that the interaction between dopamine and its receptors in the peripheral and central nervous systems results in the activation of the enzyme adenylate cyclase. The adenylate cyclase is a membrane-bound enzyme that converts adenosine triphosphate (ATP) to cyclic AMP. Cyclic AMP accumulates intracellularly and is therefore considered the "second messenger" in the process of dopaminergic synaptic transmission.

Cyclic AMP has been shown to act as a second messenger not only for dopamine, but for a variety of catecholamine neurotransmitters and peptide hormones. What then determines the specificity in the multiple actions of accumulated cyclic AMP? A large body of evidence (for recent reviews, see Greengard 1976; Rubin and Rosen 1975) supports the suggestion (Kuo and Greengard 1969) that all the physiological functions of this cyclic nucleotide are mediated and specified through a class of enzymes named cyclic AMP-dependent protein kinases. Protein kinase transfers a phosphate from ATP onto a protein to form a phosphoprotein. This process is called protein phosphorylation. When certain enzymes are phosphorylated, they convert from an inactive to an active form or vice versa. Cyclic AMP acting through protein kinases can thus induce changes in cellular activities by regulating or activating key enzymes that play a role in various cellular functions. Many different proteins can serve as substrates for protein kinases in neural tissue (Ehrlich et al. 1977*b*). It was therefore suggested that the specificity in the responses of a cell to various inputs can be determined by the existence of numerous phosphoproteins that differ in their phosphorylative response to neurohumoral stimulation (Ehrlich et al. 1977*a*; Ehrlich, Rabjohns, and Routtenberg 1977*c*; Ehrlich and Routtenberg 1974).

Protein phosphorylative activity has been directly implicated in several mechanisms involving dopaminergic transmission. Tyrosine hydroxylase, mentioned above as the rate-limiting enzyme in the synthesis of dopamine, can be activated by a phosphorylation process (Goldstein et al. 1976; Lovenberg, Bruckwik, and Hanbauer 1975). Recent studies have implicated specific membrane-bound phosphoproteins in the mechanisms of calcium-dependent neurotransmitter release from presynaptic terminals (DeLorenzo 1976). Thus, the phosphorylation of proteins can regulate important steps in the processes that determine the "supply" of presynaptically originating dopamine. The efficacy of dopaminergic synapses is determined not only by the amount of released dopamine, but also by the degree of sensitivity of postsynaptic receptors to stimulation by dopamine. On the molecular level, this can be determined by the magnitude of the adenylate cyclase response to dopamine stimulation. Gnegy, Uzunov, and Costa (1976) have demonstrated that an increase in the phosphorylation of membrane-bound proteins results in a decreased response of adenylate cyclase to dopamine activation.

Thus, the phosphorylation of proteins can regulate a multiplicity of presynaptic and postsynaptic events that are each intimately involved in the mechanism of action of dopaminergic synapses (figure 2). It is possible, therefore, that some of the aberrations in dopaminergic synaptic transmission (believed to be associated with schizophrenia) result from abnormalities in enzymatic systems that are involved in the phosphorylation of specific proteins. There is some evidence that, in addition to cyclic nucleotides, neuroactive peptides in general, and endorphins in particular, may also be involved in the regulation of the events in the phosphorylation system. Such evidence has begun to emerge from studies on the role of opiates and opiate receptors in dopaminergic mechanisms.

The Opiate Receptor and Endorphins

The breakthrough in the investigation of the mode of action of nar-

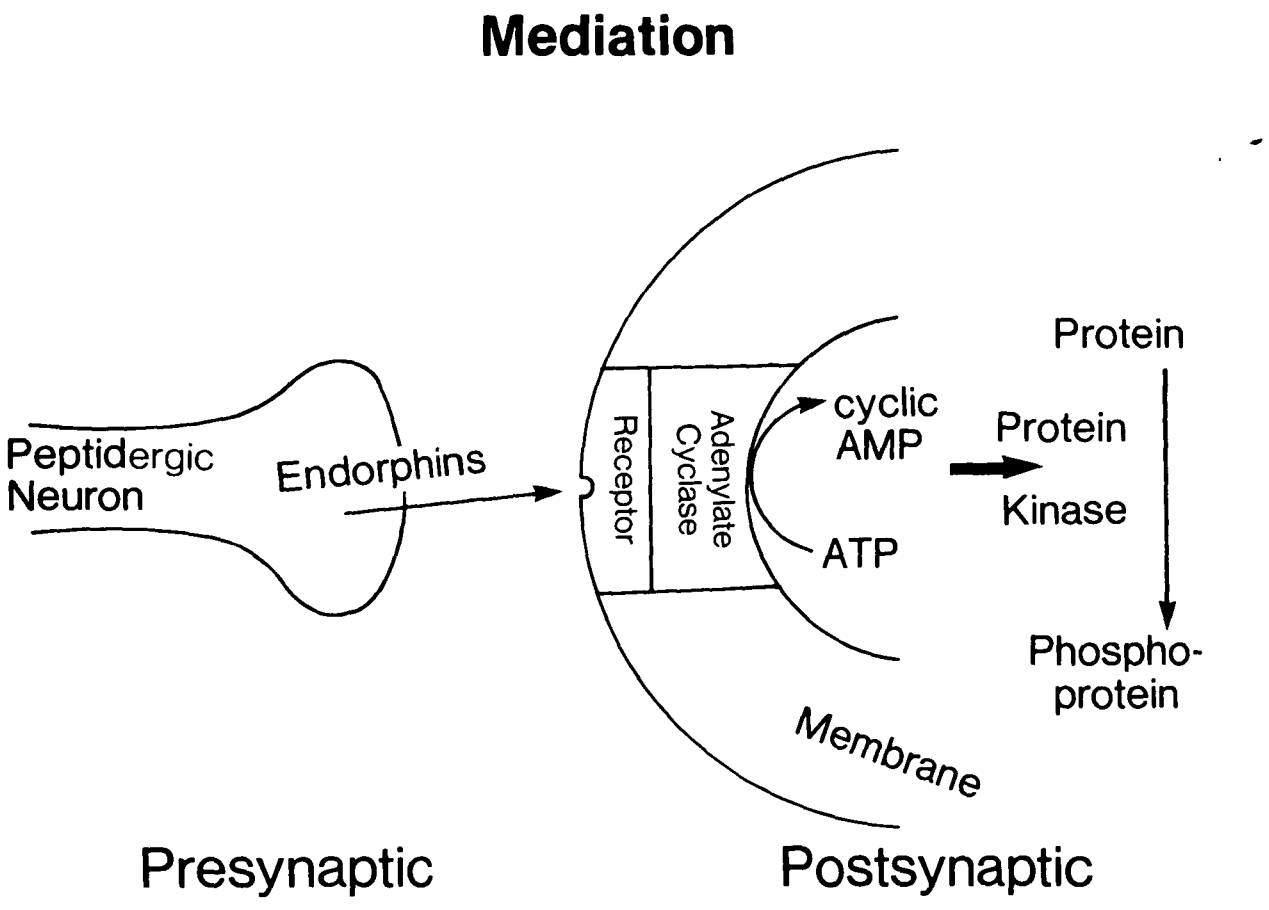


Figure 2a. Hypothetical mechanisms of endorphin action—Endorphins as neurotransmitters (mediation)

Endorphin is released from the presynaptic terminal of a peptidergic neuron and interacts with a specific receptor located on an adjacent postsynaptic membrane. This receptor may be coupled with adenylate (or guanylate) cyclase. These cyclases form, respectively, cyclic AMP or cyclic GMP. These cyclic nucleotides regulate protein kinases, which in turn transfer phosphate to proteins. Phosphoproteins then regulate numerous cellular functions.

cotic agonists was made in 1973, when three laboratories (Pert and Snyder 1973; Simon, Hiller, and Edelman 1973; Terenius 1973) simultaneously and independently discovered stereospecific opiate-binding sites in rat brain homogenates. These three groups have demonstrated that the opiate-binding sites in neuronal tissue are stereospecific, saturable, possess high affinity for opiate agonists, and that an excellent correlation exists between the binding affinity of opiates and their pharmacological potency. The discovery in brain of an endogenous substance with the capacity to bind competitively to opiate receptors and with biological characteristics mimicking those of the opiates was first reported by Hughes (1975). Similar reports from other laboratories appeared at nearly the same time (Pasternak, Goodman, and Snyder 1975; Terenius and Wahlstrom 1975). These naturally occurring opiate-like compounds in mammalian tissues were named "endorphins" as a contraction of "endogenous morphines" by Simon (1978, p. 126). Generically, all substances that are endogenous and bind to opiate receptors are re-

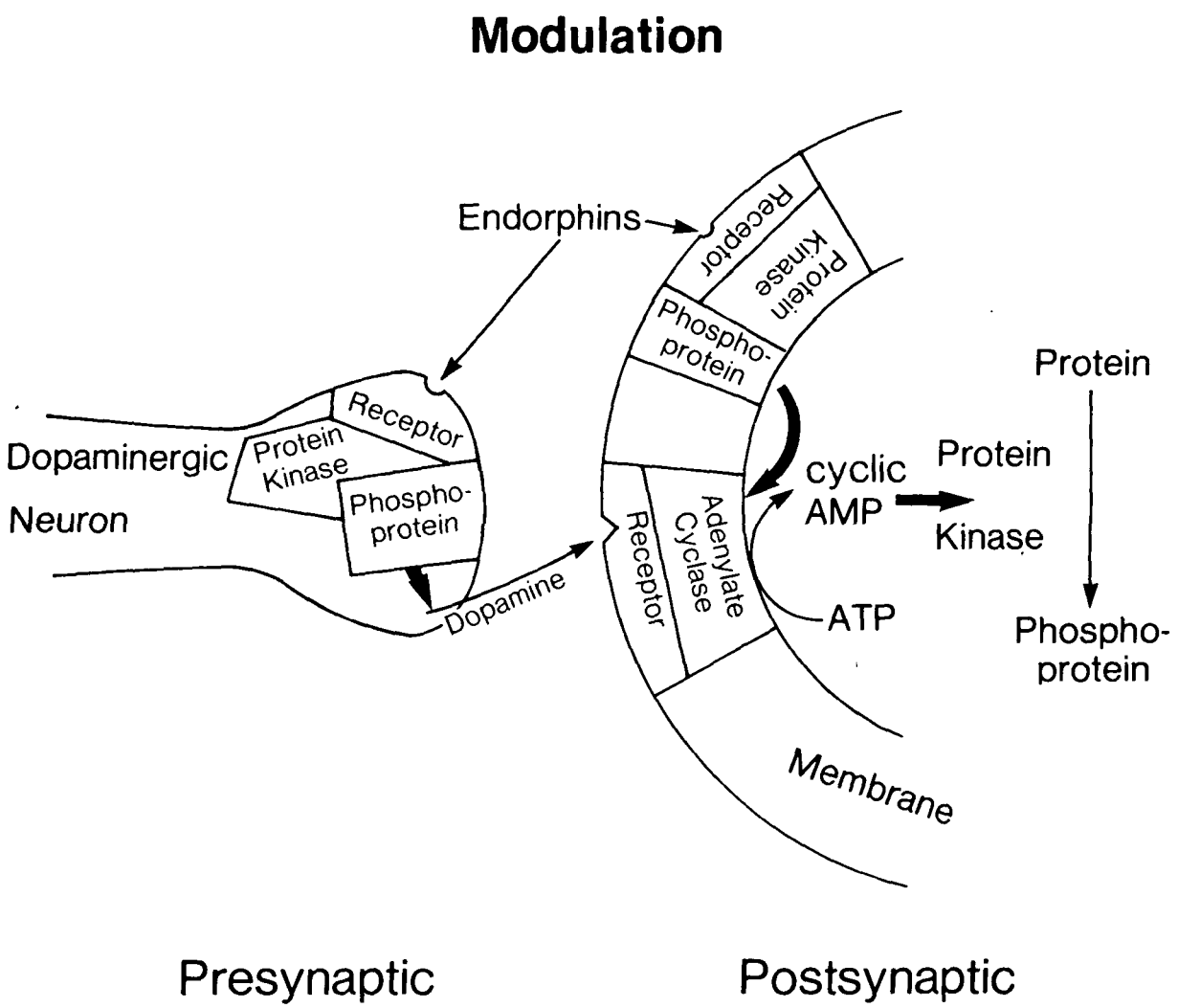
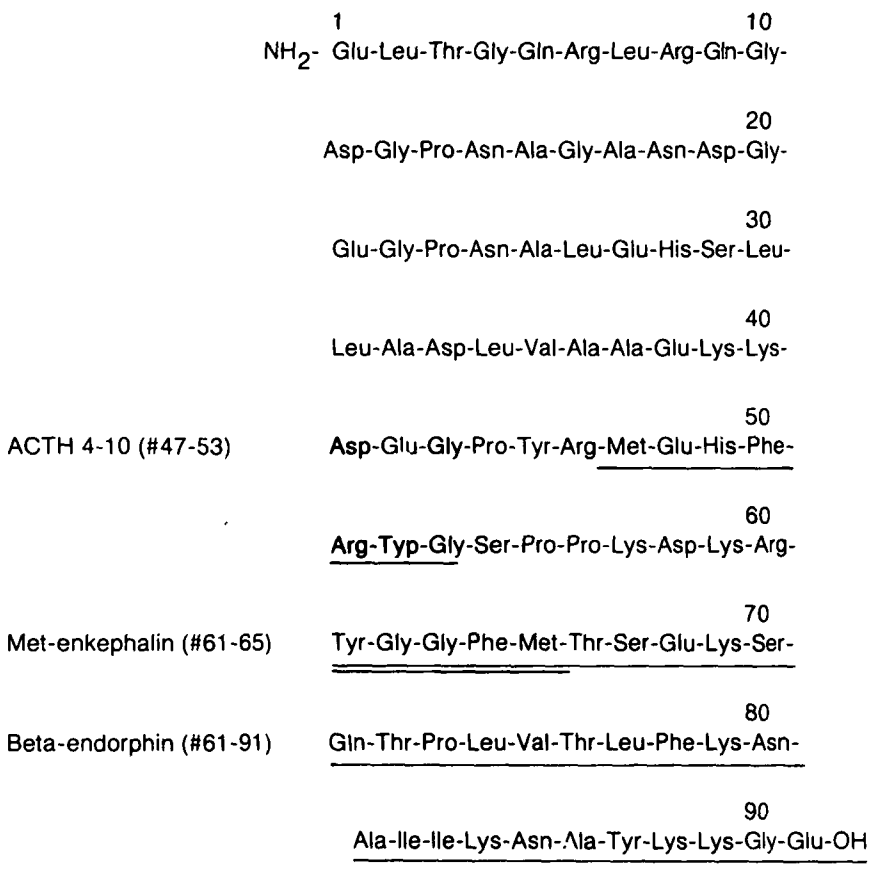


Figure 2b. Hypothetical mechanisms of endorphin action—Endorphins as neuromodulators

The figure depicts a synapse in which the neurotransmitter is dopamine. The receptor in this case is coupled with adenylate cyclase. *Endorphins act on the presynaptic receptor to inhibit dopamine release. This action may be mediated by protein kinase. Endorphins also* act on a postsynaptic receptor to change the sensitivity of the dopamine receptor This effect may also be mediated by protein kinase. Adapted from Ehrlich (1979).

ferred to as endorphins. Two of these endorphins were purified from brain and were shown to be pentapeptides (Hughes et al. 1975; Simantov and Snyder 1976); they have been designated met-enkephalin and leu-enkephalin. The met-enkephalin has a peptide sequence that is in common to part of a larger hormone, beta-lipotropin (figure 3). Another fragment of lipotropin, amino acid #61-91, is referred to as beta-endorphin. To date, no large endorphin-like molecule with leu-enkephalin as part of its sequence (as the met-enkephalin constitutes part of beta-endorphin) has been purified from brain or pituitary (Rubenstein, Stein, and Udenfriend 1978). However, leu-endorphin was reportedly isolated from the dialysate of blood of schizo-

Figure 3. Amino acid sequence of human beta-lipotropin[1]



[1] According to Li and Chung (1976).

phrenic patients (Palmour, in press). This report has so far not been confirmed. Although no current classification includes adrenocorticotropic hormone (ACTH) or its fragments as members of the "endorphin" class, they do meet the definition given above in that they are endogenous and do bind to an opiate receptor (Jacquet 1978; Terenius 1976).

Using *in vitro* assays Cox et al. (1975), Hughes (1975), and Guillemin, Ling, and Burgess (1976) found that beta-endorphin, the enkephalins, and other neuropeptide fragments of lipotropin were effective in displacing stereospecifically bound agonists to opiate receptors while other peptides were not. Additionally, the *in vivo* administration of endorphins (beta-endorphin, enkephalins, or both) demonstrated that they possess analgesic effects (Büscher et al. 1976; Graf et al. 1976; Hambrook et al. 1976; Loh et al. 1976*b*; Pert et al. 1976) and the analgesic effect was greater than that of morphine. The beta-endorphin effects were longer lasting than those produced by the pentapeptides. Cross-tolerance to analgesic effect between beta-endorphin and morphine has been reported (Van Ree et al. 1976). Cross-tolerance between morphine and met-enkephalin has been demonstrated by measuring analgesic response to met-enkephalin administration with and without morphine implants (Blasig and Herz 1976). Furthermore, beta-endorphin and met-enkephalin have been shown to produce dependence similar to morphine (Loh et al. 1976*b*; Wei and Loh 1976). These findings imply that endorphins interact with the same receptor(s) as morphine (the opiate receptor).

However, recent evidence seems to suggest the existence of two classes of receptors mediating the effects of morphine. Endorphins are the endogenous ligands for one class; ACTH may be the ligand for the other class (Jacquet 1978). Endorphins and ACTH-like peptides share the same precursor (pro-opiocortin). Furthermore, they share some behavioral effects in animals, such as excessive grooming (Gispen, Van Ree, and DeWied 1977) and extinction of active avoidance (DeWied et al. 1978). Watson et al. (1978*a*) provided an immunocytochemical demonstration of two separate opiate peptide neuronal systems, one being an enkephalin system and the other a beta-lipotropin/beta-endorphin/ACTH system.

Underlying these behavioral effects may be the interaction of endorphins with selective neuronal activities. It has been suggested that endorphins play both mediatory and modulatory roles in neural function. When endorphins act as putative neurotransmitters in a process that involves the inhibition of postsynaptic adenylate cyclase and activation of guanylate cyclase, their function is mediatory (Gispen, Van Ree, and DeWied 1977; Minneman and Iversen 1976). However, it was also shown (Barker et al. 1978*a*) that such peptides can alter the response of

neurons to the stimulatory effects of classical nonpeptide neurotransmitters. In this process the endorphins play a modulatory role. Such modulation could be carried out on the molecular level via a mechanism in which neuroactive peptides induce changes in the properties of neuronal membranes. Changes in the conformation of membranes can result in altered activity of membrane-bound enzymes such as dopamine-sensitive adenylate cyclase, which are directly involved in neuronal function. The phosphorylation and dephosphorylation of membrane-bound proteins have been reported to provide a mechanism that can induce structural alterations in membranes (Gazit, Ohad, and Logter 1976). Zwiers et al. (1976) have demonstrated that ACTH fragments have direct effects on the activity of membrane-bound protein kinases that phosphorylate specific proteins in synaptic membranes. Recent observations (Davis and Ehrlich 1978) indicate that the phosphorylation of these same proteins is also effected by met- and leu-enkephalin.

These *in vitro* experiments imply that the effects of neuroactive peptides on protein phosphorylation may modulate synaptic function *in vivo* (figure 2b). This suggestion is supported by the observations that the exposure of rats to stress (Ehrlich, Rabjohns, and Routtenberg 1977) or to chronic morphine treatment (Ehrlich et al. 1978) elicits similar changes of protein phosphorylation.

Endorphins and the Dopamine System

It appears that neurons containing endorphins may be involved in a modulatory role for the regulation of neuronal activities, particularly dopaminergic ones. Examples of peptidergic neurons modulating other neuronal pathways have been previously indicated (Barker et al. 1978; Barker, Smith, and Neale 1978*b*). The evidence for the modulatory role of endorphins is also provided by studies in which beta-endorphin was applied to brain tissue. This treatment resulted in an inhibition of the potassium-induced release of dopamine (Loh et al. 1976*a*). Besides the modulation of dopamine release, it appears that met-enkephalin elevates the rate of synthesis and turnover of dopamine and its metabolites (Biggio et al. 1978). These effects could be blocked by naloxone indicating that the modulation was through an opiate receptor rather than a dopamine receptor. In an earlier review (Lal 1976), evidence was presented that at least some of the behavioral and physiological effects of opiate agonists were produced by indirect influences on dopaminergic synaptic transmission. More recently, it has been shown that morphine-induced central stimulation can be antagonized by apomorphine, a dopamine receptor agonist (Strombom and Svensson 1978). Further support for the involvement of opiate receptors in the modulation of the dopamine system was provided by the fact that the effect of enkephalin on dopamine metabolism was still observed after kainic acid treatment, a chemical procedure to destroy dopamine receptors (Biggio et al. 1978). The major evidence for a presynaptic interaction of endorphins with dopamine cells was provided by the decrease in enkephalin-receptor binding after specific chemical lesions of dopamine cells with 6-hydroxy-dopamine (Pollard, Llorens-Cortes, and Schwartz 1977), a toxin to dopamine cells. It is important to note that although 80 percent of the dopamine cells degenerated after the lesion, or after a surgical cut of the pathway, only a 20–30 percent reduction of enkephalin binding to opiate receptors was detected. This finding certainly suggests that the enkephalin receptors occur on cells other than dopamine cells. Whether some of these receptors could be on the undegenerated postsynaptic cells is not known. However, other evidence (Bradley et al. 1976; Friedrickson and Norris 1976; Gent and Wolstencraft 1976; Hill, Pepper, and Mitchell 1976) indicates that postsynaptic influences of synaptic activity by endorphins does occur. The key question is whether receptors on the various cell types might differ in their specificity of interaction with the different endorphins. In this context, it has been shown (Gilbert and Martin 1976; Lord et al. 1977) that differences do exist between the two classically studied opiate receptor systems, the mouse vas deferens and the guinea pig ileum. We have mentioned studies suggesting that the brain also contains more than one class of morphine receptors (Jacquet 1978; Jacquet et al. 1977; Lord et al. 1977). Different receptor types in brain must not be confused with the same receptor in different brain regions. For example, met-enkephalin application to two different brain regions results in markedly different behavioral responses, such as analgesia and seizures (Frenk, McCarty, and Liebeskind 1978). These experiments point out the regionality of specific functions in brain and serve to emphasize the markedly different roles in which the same endogenous compound can participate. However, these authors also suggested that different types of receptors could exist in each brain region since in their earlier studies (Urea et al. 1977) both behaviors oc-

curred after a ventricular administration.

Of the many behavioral effects of endorphins in animals, one was thought to be particularly important in its potential implications for mental health: Rigid immobility was produced in rats by intracerebral administration of beta-endorphin (Bloom et al. 1976; Jacquet and Marks 1976). The rat rigidity was seen as an analog of human catatonia (Bloom et al. 1976). Jacquet and Marks felt that the immobility in rats was similar to the extrapyramidal rigidity elicited in patients by neuroleptics. Recent evidence indicates that this similarity goes beyond the behavioral level: Beta-endorphin-induced catalepsy was shown to be mediated by metabolite alterations in nigrostriatal dopamine neurons (Berney and Hornykiewicz 1977; Van Loon and Kim 1978).

We hypothesize that deviations of the dopaminergic transmission postulated in schizophrenia may be due to an alteration in the endorphin system. If an endorphin excess exists in schizophrenia, it could cause dopamine receptor supersensitivity. Elevated amounts of endorphins, in addition to inhibiting dopamine release (Loh et al. 1976*a*), can also cause a decreased phosphorylation of membrane proteins (Davis and Ehrlich 1978; O'Callaghan, Williams, and Clouet, in press). Each of these events can lead to receptor supersensitivity: Decreased transmitter release can cause a compensatory increase in receptor activity (Friedhoff 1977), while decreased membrane phosphorylation can result in an increased adenyl cyclase response to dopamine stimulation (Gnegy, Uzunov, and Costa 1976). Long-term morphine administration to animals elicits dopamine receptor supersensitivity (Bonnet et al. 1978) and a decreased phosphorylation of membrane proteins (Ehrlich et al. 1978), which are enkephalin-sensitive (Davis and Ehrlich 1979).

If a deficiency of endorphins occurs in schizophrenia, it may cause the same net result: a hyperactive dopamine system. This hyperactivity would develop through different biochemical mechanisms than described above. One might postulate an inability of the neurons to adjust to a deficiency of an inhibitory influence of endorphins. In essence, the system would always be "on." The mechanism would be different from receptor supersensitivity, but the ultimate effects might be identical. Although considerable evidence links the endorphins and the dopamine system, effects of endorphins on other transmitter systems are also known.

Endorphin Hypothesis of Schizophrenia

Abnormality of the endorphin system may be implicated in schizophrenia. The hypotheses tested so far deal with the potential abnormality of the ligands (i.e., endorphins); an abnormality of the endorphin receptors has also been considered (Verebey, Volavka, and Clouet 1978). The hypotheses concerning the ligands can be classified into three types: the first type postulates endorphin excess in schizophrenia, the second type postulates endorphin deficiency, and the third one postulates the presence of abnormal endorphins. This third hypothesis may overlap with the first two hypotheses. An extensive review of this material was published recently (Verebey, Volavka, and Clouet 1978); a brief recapitulation and update will be presented here.

The hypothesis of endorphin excess has received initial support from the reports of increased CSF levels of endorphins in chronic schizophrenic patients; these levels decreased after neuroleptic treatment (Terenius et al. 1976). Narcotic antagonists were used to test the hypothesis of endorphin excess. Gunne, Lindstrom, and Terenius (1977) have reported a therapeutic effect of .4 mg naloxone I.V. The effect of low naloxone doses could not be replicated (Davis et al. 1977; Janowsky et al. 1977; Volavka et al. 1977), but doses around 10 mg may be effective in a subpopulation of schizophrenics (Emrich et al. 1977; Watson et al. 1978*b*).

Another narcotic antagonist, naltrexone, was also used in therapeutic experiments in schizophrenia with negative results (Jackson and Volavka, in preparation; Mielke and Gallant 1977; Simpson, Branchey, and Lee 1977). However, naltrexone was found to possess clear morphine-like effects in opiate-naive subjects (Volavka et al. 1979), and these results therefore have no meaning for the hypothesis of endorphin excess. Thus, the hypothesis of endorphin excess is viable, and more work is needed to identify the subpopulation of schizophrenics who may respond to high doses of naloxone.

The hypothesis of endorphin deficiency may be tested directly by the administration of an endorphin. Kline et al. (1977) claim therapeutic effects of beta-endorphin in schizophrenics. Several groups are now attempting to replicate these results. Because of their fast rate of biotransformation, natural endorphins or enkephalins may not be suitable substances for clinical use. Certain molecular modifications retard that rate (DeWied et al. 1978; Roemer et al. 1977), and at least one of these new synthetic substances may be ef-

fective in schizophrenia (Verhoeven et al. 1978). If schizophrenia is related to decreased opiate receptor occupancy (which may be a consequence of endorphin deficiency), it may not matter whether endogenous or exogenous ligands are used to correct this situation (Verebey, Volavka, and Clouet 1978). That suggestion implies that the efficacy of opiate treatment for psychoses (which was common until World War II) should be reevaluated.

The hypothesis of abnormal endorphins in schizophrenia has received support from the recent work on hemodialysis. Wagemaker and Cade (1977) have seen clinical improvement in schizophrenics after hemodialysis. Palmour (in press) has analyzed the dialysate and reported the isolation of leu-endorphin—a hitherto unobserved and presumably abnormal compound, which might be a precursor of leu-enkephalin. However, according to Bloom (1978), Guillemin has also analyzed the dialysates provided by Wagemaker and was "unable to find endorphin activity in any of them" (p. 140). Obviously the exciting findings of Wagemaker, Palmour, and their colleagues require further study. Several attempts to replicate their clinical findings in controlled experiments are in progress. The hypothesis of abnormal endorphins in schizophrenia needs more testing.

We have suggested that the malfunction underlying mental illness may lie in the disordered relationship between different sets of opiate receptors (Verebey, Volavka, and Clouet 1978). An altered interaction between two classes of neuropeptide receptor systems has recently been proposed as the cause of opiate abstinence syndrome (Jacquet 1978). It is possible that further research will reveal an alteration in the integration of the neuromodulatory peptide receptor systems. That alteration may cause changes in the dopaminergic transmission, and ultimately schizophrenia (figures 1 and 2).

We emphasize that there is a substantial difference in the amounts of data supporting the proposed hypotheses. The dopamine hypothesis has received considerable support from pharmacological and clinical experiments. The role of endorphins in schizophrenia is questionable, however, and the links between endorphins and dopaminergic transmission have not been fully explored. The role of protein phosphorylation in schizophrenia has not been studied. These hypotheses can be tested, and we hope that our review will stimulate experimental investigations.

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