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 pre- 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

ENDORPHINS

OPiate RECEPTORS

CYCLIC-NUCLEOTIDES

PROTEIN-PHOSPHORYLATION

(DOPAMINERGIC)

SYNAPTIC-TRANSMISSION

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 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 post-mortem 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 affecting 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. 1977a). 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. 1977b; Ehrlich, Rabjohns, and Routtenberg 1977c; 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, Bruckwitz, 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-
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 NH2 Glu-Leu-Thr-Gly-Gln-Arg-Leu-Arg-Gln-Gly-
   10 Asp-Gly-Pro-Asn-Ala-Gly-Ala-Asn-Asp-Gly-
   20 Glu-Gly-Pro-Asn-Ala-Leu-Glu-His-Ser-Leu-
   30 Leu-Asp-Leu-Val-Ala-Glu-Lys-Lys-
   40 ACTH 4-10 (#47-53) Asp-Glu-Gly-Pro-Tyr-Arg-Met-Glu-His-Phe-
   50 Arg-Tyr-Gly-Ser-Pro-Pro-Lys-Arg-
   60 Met-enkephalin (#61-65) Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-
   70 Beta-endorphin (#61-91) Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-
   80 Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Gly-Glu-OH

1 According to Li and Chung (1976).
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 adenylylate 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 1978b). 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. 1976a). 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-
creased adenyl cyclase response to
dopamine stimulation (Gnegy, 1976).
Increased transmitter release can
cause dopamine receptor super-
sensitivity (Bonnet et al. 1978). Long-
term morphine administration to
animals elicits dopamine receptor
 supersensitivity (Bonnet et al. 1978).

If a deficiency of endorphins
occurs in schizophrenia, it may
cause the same net result: a hyper-
active dopamine system. This hyper-
activity would develop through dif-
ferent biochemical mechanisms than
described above. One might postu-
late 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 supersen-
sitivity, but the ultimate effects
might be identical. Although consid-
erable 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 schizo-
phrenia. The hypotheses tested so
far deal with the potential abnormal-
ity of the ligands (i.e., endorphins);
an abnormality of the endorphin re-
ceptors 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 ab-
normal endorphins. This third hy-
pothesis may overlap with the first
two hypotheses. An extensive re-
view of this material was published
recently (Verebey, Volavka, and
Clouet 1978); a brief recapitulation
and update will be presented here.

The hypothesis of endorphin ex-
cess has received initial support
from the reports of increased CSF
levels of endorphins in chronic
schizophrenic patients; these levels
decreased after neuroleptic treat-
ment (Terenius et al. 1976). Narcotic
agonists 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 ef-
fect 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 subgroup of
schizophrenics (Emrich et al. 1977;
Watson et al. 1978). Another narcotic
agonist, naltrexone, was also used in ther-
apeutic 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 end-
orphin 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 de-
iciency may be tested directly by
the administration of an endorphin.
Kline et al. (1977) claim therapeutic
effects of beta-endorphin in schizo-
phrenics. Several groups are now at-
tempting to replicate these results.
Because of their fast rate of bio-
transformation, 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-
ffective 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 integrity 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.

References


Gnegy, M.E.; Uzunov, P.; and Costa, E. Regulation of dopamine stimulation of striatal adenylate-cyclase by an endogenous Ca++-binding pro-


**Acknowledgments**

Some of the experimental results reported in this paper were obtained in studies supported by grants and intramural funds from the Missouri Institute of Psychiatry, University of Missouri-Columbia School of Medicine. We also thank Jill Dodds for typing and proofreading the manuscript.

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**Special Report: Schizophrenia**

Single copies of *Special Report: Schizophrenia 1976* by Samuel J. Keith et al. are available free of charge from the Center for Studies of Schizophrenia. Multiple copies will also be supplied to requesters who wish to use the report for teaching purposes. The 58-page booklet summarizes recent research in schizophrenia, with special emphasis on work carried out by investigators who have received grant support from the National Institute of Mental Health. The major research areas covered in the report are Diagnosis, Genetics, Biology, Psychophysiology, Psychological Functioning, Family Studies, Studies of Populations at High Risk, Childhood Psychoses, Borderline Conditions, and Treatment. Requests for the report should be addressed to the Center for Studies of Schizophrenia, National Institute of Mental Health, 5600 Fishers Lane, Rm. 10C-26, Rockville, MD 20857.