Biological Theories of Depression

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DEPRESSIVE DISORDERS

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Table of Contents

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Biological theories regarding the etiology of depression date back to antiquity. Hippocrates is credited with advancing one of the first biological hypotheses. He felt that the accumulation of "black bile" and phlegm affected brain functioning, "darkening the spirit and making it melancholic" (Lewis, 1967). Over the centuries, theories have continued to be proposed, often reflecting the general scientific interests and advancements of the times.

During the past quarter century, hypotheses as to the biological pathogenesis of depressive illness have rapidly evolved. Some general patterns can be discerned from this evolution. Early modern proposals emphasized a deficiency model of depressive illness in which an inadequate amount of a particular substance, such as the neurotransmitter norepinephrine, was identified as the causative factor. This deficiency model of depression probably had its roots in two types of clinical data. The first of these consisted of observations of mood states of medical patients suffering from diseases involving the deficiency of a particular neurotransmitter, vitamin, or hormone, such as occurs in patients with hypothyroidism. The second consisted of observations of depressive

reactions caused by pharmacological therapies which were thought to deplete particular substances, such as the depletion of norepinephrine stores by the antihypertensive agent reserpine (Golden & Potter, 1986).

As it became clear that the deficiency of a single substance was unlikely to account for all of the observed phenomena of depressive illnesses, and as scientists began to recognize the multitude of interactions that take place among neurotransmitter systems, the deficiency model began to yield to imbalance theories. In this revised model, the interactions and relative balance between two systems were addressed. Most recently, with the growing appreciation for the complexity of dynamic systems in the brain, and perhaps in reflection of general systems theory, hypotheses based on relatively subtle forms of systems dysregulation have come into prominence (Siever & Davis, 1985).

It is particularly challenging to develop and test biological theories of the etiology of depression. Depressive syndromes, as described elsewhere in this volume, include a constellation of symptoms that are quite "human" in character. Thus, it is much more difficult to develop an animal model or "test tube" equivalent for depression than it is for infectious or neoplastic diseases. While there are animal models for depression, they seem to be limited in capturing and quantifying some of the core, essential features of depression, including sadness, low self-esteem, and anhedonia. Also, it is

difficult, although becoming less so with newer imaging techniques, to study brain function directly in people. Practical and ethical considerations eliminate some of the usual approaches to the examination of organ systems, such as the use of biopsy. Because of the incredible complexity of the brain, isolated study of small components of the system is fraught with potential problems in "missing the forest for the trees."

The emergence of new developments in technology has influenced the types of questions that can be asked, and has shaped the development of biological theories. For example, in the mid-1960s, new techniques in chromatography permitted the measurement of very small concentrations of biochemical compounds. Not coincidentally, theories regarding the role of catecholamine neurotransmitters, whose metabolites could by then be measured in body fluids, began to emerge. In the 1970s and 1980s, increasingly sophisticated techniques, including radioimmunoassays, pushed back the limit of quantification of biological compounds to incredibly minute concentrations. This development permitted the accurate measurement of various hormones whose extremely low concentrations could not be measured previously. This in turn allowed researchers to advance and test theories regarding the possible roles that various neurohormones and other trace compounds might play in the pathophysiology of depression. Currently, the technologies of molecular biology and brain imaging are developing and becoming widely available at

an explosive pace. We predict that theories of depression in the 1990s will be shaped, in part, by the perspectives and insights that are offered by these techniques.

In this chapter, we present a review of selected biological theories of depression. Rather than presenting every theory, we have chosen for elaboration three biochemical hypotheses which have undergone repeated testing, modification, and retesting over many years and which continue to have heuristic value.

NOREPINEPHRINE

For more than half a century, the catecholamine norepinephrine has been recognized as a stress-related hormone. Cannon (1929) identified norepinephrine (also referred to as “noradrenaline”), along with epinephrine, as playing a key function in mobilizing the “fight-flight” response to threatening stimuli. Hans Selye later documented the role of norepinephrine in the physiological response to stress (Selye, 1950). After it was established that norepinephrine fulfilled the requirements for being a central neurotransmitter, this biogenic amine became a cornerstone in biological theories of depression.

The catecholamine hypothesis of affective illness was first articulated more than 25 years ago (Bunney & Davis, 1965; Prange, 1964; Schildkraut, 1965). In its original formulation, it proposed that “some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly noradrenaline, at functionally important receptor sites in the brain. Elation, conversely, may be associated with an excess of such amines” (Schildkraut, 1965). Much of the impetus for this hypothesis was originally based on the application of the “pharmacological bridge” paradigm in which clinically effective antidepressants, including the monoamine oxidase inhibitors and the tricyclic compounds, were noted to increase the availability of norepinephrine at brain synapses. From this

observation, the pathogenesis of depression was assumed to be caused by a deficiency in available central norepinephrine prior to treatment. The catecholamine hypothesis also derived support from the observations of the mood-altering effects of the antihypertensive medication reserpine. This compound, which was reported to cause depressive reactions in a number of patients receiving treatment for high blood pressure, was found to deplete norepinephrine from synaptic storage vesicles.

As the original catecholamine hypothesis came under close examination, some questions and problems emerged. First, compounds that were expected, according to the hypothesis, to function as antidepressants were not found to be clinically effective. For example, cocaine and amphetamines were noted to increase central noradrenergic neurotransmission, yet were not effective medications in treating depression. Second, the validity of the original observation that reserpine caused depression came into question. A critical review of the literature by Goodwin, Ebert, and Bunney (1972) suggested that reserpine was associated with "pseudo-depression"—lethargy and sedation— rather than true clinical depression, in most of the reported cases. The 5 to 9 percent of patients who developed the full depressive syndrome while receiving this medication frequently had prior histories of depression, suggesting that the biological effects might be "unmasking" an underlying depressive illness, rather than causing its development de novo. More recently, the

controversy regarding the putative depressogenic effects of decreased central noradrenergic neurotransmission has centered on propranolol and other antihypertensive agents which block beta-adrenergic receptors. Some reports support the claim that these compounds cause depression (Avorn, Everitt, & Weiss, 1986; Mattiasson & Henningsen, 1978; Petrie, Maffucci, & Woolsey, 1982; Waal, 1967), others do not (Adler & New York VAMC Study Group, 1988). Our own studies of healthy subjects without prior personal or family histories of depression suggest that propranolol can induce some, but not all, of the clinical stigmata of depression in normal subjects (Golden, Brown, et al., 1989).

Another problem with the original catecholamine hypothesis relates to the observed "lag time" in antidepressant response. Antidepressant pharmacotherapies require two to six weeks before a significant clinical response is achieved, yet the biochemical effects, including increased availability of norepinephrine, occur almost immediately upon initiation of treatment. Also, several of the "second generation" antidepressants, such as fluoxetine, do not affect norepinephrine to any appreciable degree, but are still clinically effective (Golden, Brown, Miller, & Evans, 1988).

Despite these challenges, the original catecholamine hypothesis has retained its heuristic value and has continued to undergo modification. Several new approaches have been applied to the study and testing of

refined versions. The major metabolite of norepinephrine, MHPG, has been studied in the urine. Maas, Fawcett, and Dekirmenjian were the first to report decreased urinary excretion of MHPG (1968), and some, but not all, subsequent investigations have confirmed this finding. Bipolar patients demonstrate this finding most consistently, perhaps in reflection of the relative homogeneity of this group. Studies of unipolar patients have produced less consistent findings, and Schatzberg's group has demonstrated both low and high MHPG-excreting subpopulations of unipolar depressives (Schatzberg et al., 1982). It is difficult to interpret the meaning of these observations, since the estimates of the actual proportion of MHPG that originates in the brain, rather than in the peripheral sympathetic nervous system, range from 80 percent (Ebert & Kopin, 1975) down to 20 percent (Blombery, Kopin, Gordon, Marley, & Ebert, 1980).

Norepinephrine itself has been measured in plasma. Early studies found norepinephrine plasma levels were elevated not only in depressed patients (Esler et al., 1982; Lake et al., 1982; Wyatt, Portnoy, Kupfer, Snyder, & Engelmann, 1971), but in manic patients as well (Lake et al., 1982). More recently, investigators have measured the plasma norepinephrine response to a physiological "orthostatic challenge test" paradigm, in order to examine the efficiency of the noradrenergic system. In rising from a supine to an upright position, depressed patients are able to maintain cardiovascular output, but require a greater increase in plasma

norepinephrine concentrations compared to healthy subjects (Rudorfer, Ross, Linnoila, Sherer, & Potter, 1985). This "inefficiency" in regulating the cardiovascular system might also be present in the noradrenergic regulation of mood in these patients, with "normal" amounts of norepinephrine being inadequate to maintain euthymic mood.

Several studies have suggested that antidepressant treatments increase the efficiency of norepinephrine systems in depressed patients. For example, such perse treatments as electroconvulsive therapy, lithium, the monoamine oxidase inhibitor clorgyline, the tricyclic antidepressant desipramine, the unicyclic aminoketone bupropion, and the serotonin reuptake inhibitor zimelidine all decrease "whole body norepinephrine turnover," that is, the 24-hour production and elimination of norepinephrine and its metabolites (Golden, Rudorfer, Sherer, Linnoila, & Potter, 1988; Linnoila, Karoum, Calil, Kopin, & Potter, 1982; Linnoila, Karoum, & Potter, 1982; Linnoila, Karoum, Rosenthal, & Potter, 1983; Rudorfer et al., 1984). Furthermore, we have shown that desipramine, monoamine oxidase inhibitors, and the unicyclic aminoketone bupropion increase the output of the hydroxylated metabolite of melatonin, a neurohormone whose release is regulated by norepinephrine, while at the same time decreasing whole body norepinephrine output (Golden, Markey, Risby, Cowdry, & Potter, 1988). Again, as with the orthostatic challenge test, these data suggest that the physiological efficiency of norepinephrine

systems in depressed patients is enhanced following treatment (Golden & Potter, 1986).

Both norepinephrine and MHPG have been studied in the cerebrospinal fluid (CSF) of depressed patients, as well as in urine and blood. These CSF studies have been inconclusive, as have direct measures of norepinephrine in autopsied brain tissue (see Willner, 1985, for review).

Studies of noradrenergic receptors and their responsivity to pharmacological "challenge" have provided yet another means for testing hypotheses regarding norepinephrine and depression. Beta-adrenergic receptors on lymphocytes provide a model for studying one type of norepinephrine receptor that is far more readily accessible than receptors in the brain. A number of studies have reported decreased responsivity to noradrenergic agonist stimulation in lymphocyte beta-adrenergic receptors in depressed patients (Extein, Tallman, Smith, & Goodwin, 1979; Mann et al., 1985; Pandey, Sudershan, & Davis, 1985). Pharmacological "challenge" paradigms have utilized the pituitary neuropeptide, growth hormone, since its release is mediated via postsynaptic alpha-2 noradrenergic receptors. Several studies have demonstrated blunted growth-hormone response to the alpha-2 agonist, or stimulating agent, clonidine in depressed patients compared to healthy control subjects (Charney etal., 1982; Checkley, Slade, & Shur, 1981; Matusseketal., 1980;Siever et al., 1982). Further, the growth-

hormone response to desipramine, the tricyclic norepinephrine reuptake inhibitor, appears to be blunted in unipolar and bipolar depressed patients compared to healthy subjects (Sawa, Odo, & Nakazawa, 1980) and in acutely depressed patients compared to patients with affective illness in remission (Calil et al., 1984).

Another approach to testing the catecholamine hypothesis of depression involves the observation of the effects of pharmacological manipulation of central noradrenergic systems in depressed patients. For example, tyrosine, the amino acid precursor for catecholamine formation, has been reported to have some antidepressant activity (Gelenberg, Gibson, & Wojcik, 1982). Also, the beta-2 agonist salbutamol has shown clinical efficacy in at least one study (Belmaker, Lerer, & Zohar, 1982).

In summary, although the original formulations of the catecholamine hypothesis of depression have required modification, the role of norepinephrine in the pathogenesis of affective illness continues to merit attention and further study.

THE CHOLINERGIC-ADRENERGIC BALANCE HYPOTHESIS

In 1972, Janowsky, El-Yousef, Davis, and Sererke proposed a cholinergic-adrenergic balance hypothesis of affective illness. This hypothesis was based, in part, on the recognition that there is extensive cholinergic innervation of brain centers in the limbic system that appear to be functionally important in the regulation of mood states. The balance hypothesis postulated that affective states may represent the relative balance between cholinergic and adrenergic activity in relevant brain areas. Specifically, a relative increase in cholinergic versus noradrenergic activity could lead to clinical depression, while a relative hyperactivity of norepinephrine versus acetylcholine could lead to mania (Janowsky et al., 1972).

A substantial body of data, including clinical observations, animal studies, and controlled clinical research, supports the role for adrenergic-cholinergic balance in the regulation of mood. Outside of the central nervous system, norepinephrine-acetylcholine interactions modulate the functioning of several other important autonomic physiological systems, including the cardiovascular, gastrointestinal, and pupillary nervous systems. As described in the previous section, many anticatecholaminergic medications, such as reserpine and propranolol, have been linked with depressive symptoms, and interestingly, these medications have central

and peripheral cholinomimetic properties in addition to their antiadrenergic activity. In animals, reserpine causes parasympathetic somatic effects, including salivation, lacrimation, miosis, diarrhea, akinesia, and tremor, as well as behavioral effects such as decreased locomotor activity, sedation, and decreased self-stimulation. In some people, reserpine is associated with a psychological profile that resembles some aspects of a depressive episode, including dysphoria, lethargy, anergy, sleepiness, and nightmares.

Perhaps the most striking evidence in support of the cholinergic-adrenergic balance hypothesis stems from observations of the psychological effects of cholinesterase inhibitors, which enhance cholinergic activity by retarding the degradation of acetylcholine. In the 1950s and 1960s, several research groups studied depressed and manic patients, and normal subjects who had been accidentally or experimentally exposed to insecticides containing cholinesterase inhibitors. In each instance, these cholinomimetic compounds seemed to induce anergic-inhibitory effects as well as to intensify and induce depressive symptoms (Bowers, Goodman, & Sim, 1964; Gershon & Shaw, 1961; Rowntree, Neven, & Wilson, 1950). The centrally active cholinesterase inhibitor physostigmine was found to induce a dramatic, albeit brief reduction in manic symptoms in bipolar patients, while placebo and neostigmine, a cholinesterase inhibitor that acts peripherally but does not cross the blood

brain barrier, caused no such effect. Physostigmine also can switch manic patients, as well as depressed patients, into a more psychomotorically retarded depressed state (Janowsky, El-Yousef, Davis, & Sererke, 1973b; Janowsky, David, El-Yousef, & Davis, 1974). This finding has been replicated by others (Davis, Berger, Hollister, & DeFraites, 1978) and extended to include schizoaffective patients and euthymic bipolar patients maintained on lithium. More recently, Risch and colleagues described depressive reactions to physostigmine in normal volunteers (Risch, Cohen, Janowsky, Kalin, & Murphy, 1981).

Acetylcholine precursors (choline, lecithin, and deanol) have been shown to induce depressed mood. Two independent groups of researchers reported an increase in depressive symptoms in schizophrenic patients who were receiving choline for treatment of tarpe dyskinesia (Davis, Hollister, & Berger, 1979; Tamminga, Smith, Chang, Haraszti, & Davis, 1976). Casey (1979) has described depressed mood, and in some cases hypomania, in a minority of patients with tarpe dyskinesia treated with deanol, the presumed acetylcholine precursor. Others have described depressive reactions to choline and to lecithin in a small number of patients receiving experimental treatment with these compounds for Alzheimer's disease. Furthermore, Cohen, Miller, Lipinski, and Pope (1980) observed anti-manic responses to choline in a group of bipolar patients.

The depressogenic effects of various cholinomimetic drugs may be somewhat specific to patients with affective disorders. Janowsky et al. (1974) observed that while nearly all psychiatric patients developed an inhibitory or anergic syndrome in response to physostigmine challenge, patients with depression, mania, or schizoaffective diagnoses became significantly more sad and depressed, compared to schizophrenic patients. More recently, in a study of a group of carefully diagnosed psychiatric inpatients, the dysphoric and behavior-inhibiting response to intravenous physostigmine was considerably more pronounced in patients with affective disorders than in psychiatric patients with other diagnoses (Risch, Kalin, & Janowsky, 1981). Also, in the study of the effects of deanol on patients with tarpe dyskinesia, referred to above, Casey (1979) noted that the subgroup of patients with a strong history of affective disorders selectively accounted for most of the depressive response to this cholinomimetic.

One of the most widely studied and established biological markers of depression is decreased rapid eye movement (REM) sleep latency (Gillin et al., 1984). REM latency is the period of time from the onset of sleep to the initiation of the first REM period. Interestingly, REM latency can be decreased by acetylcholine and increased by norepinephrine. Depressed patients have a greater sensitivity to the effects of a cholinergic agonist on this sleep parameter. Following infusion of the acetylcholine agonist

arecholine, the REM latency of depressed patients decreased to a greater degree than that of healthy subjects (Sitaram, Nurnberger, Gershon, & Gillin, 1980). This increased sensitivity to cholinergic effects was also seen in the first-degree relatives of depressed patients and in patients with anorexia nervosa who had past histories of depression (Sitaram et al., 1980). Using another agonist challenge paradigm, Sitaram, Gillin, and Bunney (1984) demonstrated another example of cholinergic hypersensitivity in depressed patients, that of exaggerated pupillary constriction following the instillation of the cholinergic agonist pilocarpine into the eyes of depressed patients, compared to healthy control subjects.

A pharmacological-behavioral approach has also been utilized in testing the cholinergic-adrenergic balance hypothesis. Stereotypic behaviors can be induced in rats by the psychostimulant methylphenidate, presumably via increased catecholaminergic activity. These methylphenidate-induced stereotypes can be antagonized by the cholinomimetic physostigmine. Similarly, methylphenidate can induce psychomotor stimulation in manic patients, including increased talkativeness, euphoric mood, and increased interpersonal interaction, and these methylphenidate-induced symptoms can be rapidly antagonized by physostigmine administration. Conversely, physostigmine can precipitate inhibitory-depressant effects, which can be reversed by methylphenidate (Janowsky, El-Yousef, Davis, & Sererke, 1973a).

While cholinomimetic drugs can produce mood-lowering and anti-manic effects, centrally acting anticholinergic drugs can stimulate mood elevation. Anticholinergic antiparkinsonian medications, used to treat neuroleptic-induced parkinsonian side effects, can cause euphoria, a sense of well being, increased sociability, and a reversal of depressed mood. Furthermore, case reports describe antidepressant responses to high doses of atropine and to other anticholinergic compounds such as biperiden and trihexylphenidyl; a recent report, a tricyclic antidepressant-induced anticholinergic syndrome led to alleviation of depressive symptoms. Finally, a number of tricyclic antidepressants have substantial anticholinergic properties, although some of the second-generation antidepressants, such as trazodone and fluoxetine, do not (Janowsky et al., 1983).

Neuroendocrine studies have also been applied to the cholinergic-adrenergic balance hypothesis. Physostigmine increases serum ACTH and beta-endorphin concentrations, and these responses are exaggerated in depressed patients (Janowsky et al., 1983; Risch, Kalin, & Janowsky, 1981).

Finally, genetic studies have also examined the cholinergic-adrenergic balance hypothesis. Nadi, Nurnberger, and Gershon (1984) reported that the cultured Fibroblasts of bipolar affective disorder patients and their relatives with affective disorders showed increases in muscarinic binding,

compared to their nonaffectively ill relatives and to healthy controls. Such "up-regulation" of cholinergic receptors could account for increased sensitivity to acetylcholine. However, other groups have been unable to replicate these results (Kelsoe et al., 1985, 1986).

Thus, considerable evidence from a variety of approaches supports the cholinergic-adrenergic balance hypothesis of affective illness. Ongoing studies should permit the development of an even greater understanding of the role of these mechanisms in affective disease processes.

SEROTONIN

While American psychiatrists were focusing their attention on the catecholamine hypotheses of depression in the early 1960s, their British colleagues were pursuing the link between affective illness and the indoleamine neurotransmitter serotonin. The indoleamine hypothesis held that a deficiency or functional deficit in central serotonin could lead to the emergence of depressive illness (Coppen, Shaw, Malleson, Eccleston, & Gundy, 1965). Some of the original observations that supported the catecholamine hypothesis were also consistent with an indoleamine hypothesis of depression. For example, the first clinically effective antidepressants—the monoamine oxidase inhibitors and the tricyclic reuptake inhibitor imipramine—increased the availability of serotonin, as well as norepinephrine, in the brain. Coppen, Shaw, and Farrell (1963) reported that the addition of tryptophan, the amino acid precursor for serotonin formation, to pharmacotherapy with a monoamine oxidase inhibitor increased clinical effectiveness in treating depression. Other psychiatrists reported some clinical utility in administering tryptophan alone as an antidepressant. When Prange and his coworkers observed that tryptophan was effective in treating mania, they revised the indoleamine hypothesis and postulated a “permissive hypothesis” of affective illness. This theory suggested that a deficit in central serotonergic neurotransmission permits the emergence of affective illness. When

coupled with decreased noradrenergic activity, depression will develop; and mania will emerge from increased noradrenergic activity in the context of decreased serotonin (Prange, Wilson, Lynn, Alltop, & Stikeleather, 1974).

Several lines of evidence support the role of a functional deficit in serotonin in depressive illness. Postmortem studies of depressed patients and suicide victims have found reduced levels of serotonin or its metabolites (Beskow, Gottfries, Roos, & Winblad, 1976; Bourne, Bunney, & Colburn, 1968; Cochran, Robins, & Grote, 1976; Lloyd, Farley, Deck, & Horneykieweiz, 1974; Shure, Campes, & Eccleston, 1967), increased serotonin-2 (5-HT2) receptor binding (Mann, Stanley, McBride, & McEwen, 1986), and decreased tritiated imipramine binding (Stanley & Mann, 1983) in brain tissue, all suggestive of decreased functional serotonergic activity. Depressed patients have decreased CSF concentrations of the serotonin metabolite 5-HIAA (Asberg & Bertilsson, 1979; Asberg, Thoren, & Traskman, 1976; Ashcroft et al., 1966; Cowdry & Goodwin, 1978), although some investigators have been unable to replicate this finding (Murphy, Campbell, & Costa, 1978). Platelets, which share several biochemical and pharmacological properties with serotonergic nerve endings, have abnormal tritiated imipramine binding (Briley, Langer, Raisman, Sechter, & Zarifian, 1980; Paul, Rehavi, Skolnik, Ballenger, & Goodwin, 1981), reduced serotonin uptake (Meltzer, Arora, Baber, & Tricou, 1981; Tuomisto & Tukiainen, 1976), aberrant seasonal variations in serotonin uptake

(Malmgren, Aberg-Wistedt, & Martensson, 1989), and supersensitivity to serotonin (Brusov et al., 1989) in depressed patients, compared to control subjects.

Treatment studies also support the role of serotonin in the pathogenesis of depression. Coppen's finding of tryptophan potentiation of monoamine oxidase inhibitor antidepressant activity has been extended to include potentiation of other monoamine oxidase inhibitors and the tricyclic antidepressant clomipramine (Glassman & Platman, 1969; Walinder, Skott, Carlson, Nagy, & Roos, 1976). Another serotonin precursor, 5-hydroxytryptophan (5-HTP), has been shown to enhance the efficacy of antidepressants and on occasion to be effective as an antidepressant itself (Carroll, 1971; Kaneko, Kumashiro, Takahashi, & Hoshino, 1979; Van Praag & Van Korf, 1974). The drug *p*-chlorophenylalanine, which decreases serotonin synthesis, has been shown to induce a recurrence of depressive symptoms in recovered patients receiving antidepressant treatment (Shopsin, Friedman, & Gershon, 1976).

Pharmacological "challenge" tests have also been applied to the serotonin hypothesis of depression. Analogous to the challenge paradigms for norepinephrine described above, these involve the administration of drugs with selective serotonergic activity and the measurement of accompanying changes in plasma concentrations of hormones whose

release is regulated by serotonin. For example, the prolactin response to IV administration of tryptophan is blunted in depressed patients (Heninger, Charney, & Sternberg, 1984), and normalizes following treatment with tricyclic antidepressants, monoamine oxidase inhibitors, and lithium (Charney, Heninger, & Sternberg, 1984; Price, Charney, Delgado, & Heninger, 1989; Price, Charney, & Heninger, 1985). Fenfluramine, a serotonin-releasing agent and uptake inhibitor, yields a blunted prolactin response in depressed patients as well (Siever, Murphy, Slater, De La Vega, & Lipper, 1984). We have recently found a blunted prolactin—as well as an ACTH—response to IV administration of clomipramine, the relatively specific serotonin uptake inhibitor, in depressed patients, compared to healthy control subjects (Golden, Hsiao, & Potter, 1989). In contrast, Meltzer's group has described an exaggerated cortisol response to the serotonin precursor 5-hydroxytryptophan (Meltzer, Umberkoman-Wiita et al., 1984); the magnitude of the cortisol response was significantly correlated with severity of depression and with suicidal activity (Meltzer, Perline, Tricou, Lowy, & Robertson, 1984). Interestingly, the exaggerated cortisol response to 5-hydroxytryptophan was seen in manic patients as well, consistent with the permissive hypothesis of affective illness described above.

Despite the wealth of supportive evidence for an indoleamine hypothesis of depression, there are limits to the conclusions that can be

drawn. Not all of the findings have been consistently replicated (e.g., low CSF 5-HIAA in depressed patients). Each of the challenge paradigms described above is less than perfect in regard to specificity for serotonergic systems (Van Praag, Lemus, & Kahn, 1987). Still, the serotonin hypothesis continues to be the stimulus for increasingly sophisticated research into the biological bases of depression.

OTHER HYPOTHESES

We have reviewed selected biological theories of depression which have significant historic value as well as continued importance in the present. Many other theories regarding the biology of depressive illness are also stimulating ongoing studies. As new neurotransmitters are discovered, their possible role in affective illness and other psychiatric syndromes comes under investigation, and there are a number of peptides, as well as additional biochemical compounds, which have been recently implicated in the pathophysiology of depression (Janowsky, Golden, Rapaport, Cain, & Gillin, 1988). For example, the dopamine hypothesis of affective illness proposes that mania is associated with increased dopaminergic neuronal activity, while depression, particularly depression with psychomotor retardation, is associated with a decrease in dopaminergic activity (Willner, 1985). Phenylethylamine, an endogenous amphetamine-like monoamine, has been postulated to be involved in depression (Sabelli & Moswaim, 1974), as has the inhibitory amino acid neurotransmitter gamma-aminobutyric acid (Berrettini & Post, 1984). Recent investigations have begun to explore the possible relationship between endorphin function and affective disorders (Emrich, Vogt, & Herz, 1983). Furthermore, theories involving biological rhythms, including sleep and seasonal cycles, have now emerged (Sack & Wehr, 1988).

SUMMARY

Several lines of evidence suggest that the classic neurotransmitters, norepinephrine, acetylcholine, and serotonin, play important roles in the pathogenesis of depressive illness. Other biochemical compounds and peptides may also be involved in the etiology of some forms of mood disorders.

With so many biological theories of depression to choose from, one might wonder which theory will ultimately turn out to be the correct one. We believe the answer is that no one theory will completely explain the biological bases for depression because depression is really a syndrome, rather than a specific unitary disease state. Although we have made some progress in identifying certain subtypes (e.g., bipolar depression), we probably still are left with many overlapping entities that currently cannot be distinguished clinically from one another. Further, because it is so difficult in clinical practice to delineate depression from related disorders, let alone isolate the possible subtypes of depression, it should not be surprising that a consistent biological correlate or marker has not yet been identified. Furthermore, it is highly likely that many biological hypotheses overlap each other, and that different neurotransmitter systems interact with each other. Still, our understanding of the biology of affective illness continues to grow at a rapid pace, and we hope that this increased

understanding will continue to be translated into more effective treatment for patients who are suffering from depression.

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