Key Words: neurobiology, depression, neurotransmitters, monoamines, serotonin, norepinephrine

Recent Advances in the Neurobiology of Depression

By Charles B. Nemeroff, MD, PhD

ABSTRACT *~ Elucidation of the neurobiological basis of depression and other mood disorders is rapidly increasing. Considerable experimental and clinical evidence supports the fundamental roles of serotonin and norepinephrine, as well as the interactions between these systems in the etiology of depression. Substantial evidence has accrued, including changes in neurotransmitter and neurotransmitter metabolite concentrations, reuptake sites, and receptors, to support the hypothesis that alteration in neuronal serotonergic and noradrenergic function occurs in the central nervous system of patients with major depression. Serotonin and norepinephrine represent the major targets of current therapeutic interventions, which may induce longer-term adaptive changes via modulation of the activity of these neurotransmitters. In addition, two neuropeptide neurotransmitters—substance P and corticotropin-releasing factor—have been implicated in the pathophysiology of mood disorders. Preliminary studies have reported the clinical efficacy of a tachykinin NK_1 receptor antagonist and a CRF_1 receptor antagonist in depressive disorders. Further clarification of the precise neurobiological changes occurring in depression has implications for the use and development of novel effective treatments for this disorder.* Psychopharmacology Bulletin. *2002;36(Suppl 2):6-23*

Introduction

The role of dysregulated neurotransmitter/neuroregulator systems in the pathophysiology of depression has been the focus of intensive investigation since the seminal publication of the catecholamine hypothesis of affective disorders nearly 40 years ago.[1] The majority of subsequent hypotheses suggest that depression arises from the dysregulation of one or more neurotransmitters or neuroregulators in areas of the brain involved in mood regulation, eg, the cerebral cortex and limbic system.[2,3] The heritability of depression suggests that, in some patients, there is a genetic predisposition to the development of this altered neurobiology.

The identification of the putative biological substrates of depression utilizes the criteria first described by Barchas and colleagues[4] (Table 1). The application of these criteria has implicated the involvement of several neuroregulators in the development of depression. Particularly strong evidence exists for a preeminent role of the monoamine neurotransmitters serotonin (5-HT), norepinephrine (NE), possibly

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dopamine (DA), and the neuropeptide corticotropin-releasing factor.[3,5-7] Some evidence also exists for a role of substance P in depressive disorders.[8] Furthermore, recent research has suggested that the neurobiology of depression may involve adaptation of a variety of neural systems.[9] The function of intracellular cascades initiated by the actions of neurotransmitters may therefore be altered in depression, leading to downstream changes in neural function.

This article will review the evidence for the involvement of monoamine and peptide neurotransmitters in the etiology of depression, and consider how an increased understanding of the neurobiology of depression may eventually impact the choice of effective treatments for this disorder.

MONOAMINES

5-HT, NE, and DA, are widely distributed neurotransmitter systems in the mammalian central nervous system, regulating a considerable array of behaviors including mood, appetite, cognition, libido, anxiety, and aggression, just to name a few. Some of the physiological and behavioral arenas attributed to the monoamines with their overlap in function are summarized in Figure 1. A number of the roles can be ascribed to individual neurotransmitters. For example, stress responsiveness, energy, and socialization have primarily been associated with NE circuits, impulsivity with 5-HT systems, and motivation and reward with DA projections. However, as noted in Figure 1, there is considerable overlap between functions of the monoamines, such that NE and 5-HT are important in anxiety responses, NE and DA in motivation, and DA and 5-HT in

TABLE 1

CRITERIA FOR LINKING NEUROREGULATORS TO A SPECIFIC PSYCHIATRIC DISORDER

A neuroregulator can be linked to a psychiatric disorder if:

- It is an endogenous substance, which alters neuronal function or for which receptors exist in nerve cells.
- It has a characteristic pattern of activity, which occurs in relation to the psychiatric disorder.
- Alteration of neuronal system activity involving one or more neuroregulators, or the balance between them, affects the psychiatric disorder.
- Appropriate manipulation of the neuroregulator system(s) induces the psychiatric disorder.
- Appropriate restoration of neuroregulator activity, or balance of activity, ameliorates the psychiatric disorder (unless the physiological process is irreversible).

Adapted from: Barchas JD, Akil H, Elliott GR, Holman RB, Watson SJ. Behavioral neurochemistry: neuroregulators and behavioral states. *Science*. 1978;200:964-973.

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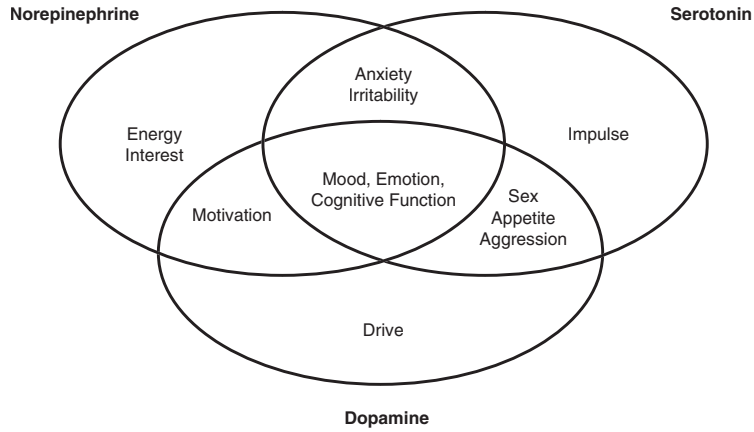
sexual behavior, appetite, and aggression. All three monoamines are important in the regulation of mood, emotion, and cognitive function. Many of these functions have been demonstrated to be impaired in patients with depression. The implication that dysfunction of monoamine systems may be involved in the etiology of depression has been the subject of considerable research, and the evidence generated to support this hypothesis will be reviewed briefly.

Serotonin

Serotonin mediates inhibitory and excitatory neurotransmission throughout the central nervous system.[3] From cell bodies concentrated in the dorsal and caudal raphe nuclei, widespread serotonergic projections extend to a considerable variety of brain areas believed to be associated with the symptoms of depression, including the hypothalamus, amygdala, cortex, hippocampus, basal ganglia, and brainstem. The serotonergic system is therefore anatomically well situated to mediate the signs and symptoms of depression, because these are so diverse that they could not possibly be mediated by just one brain region. For example, the hypothalamus is likely to be involved in appetite disturbance, the cerebral cortex and hippocampus in cognitive dysfunction, and the brainstem with sleep disturbance, all of which are associated with depression. The effects of serotonin are mediated through 5-HT receptors, of which at least 13 molecular subtypes are present, including three major receptor families (5-HT_{1A}, 5-$HT_{2A/C}$, and 5-HT_3).[10] Receptors are present at pre- and postsynaptic sites, in addition to their location on serotonergic nerve-cell bodies.

FIGURE 1

THE INTER-RELATIONSHIP OF SOME PHYSIOLOGICAL AND BEHAVIORAL RESPONSES MEDIATED BY MONOAMINE NEUROTRANSMITTERS



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Dysfunction in the serotonergic system is a well-established theory explaining the pathophysiology of depression.[3,11] There is overwhelming evidence indicating a relative deficiency of 5-HT in most or all forms of depression.[11] This evidence has been obtained from neuroendocrine studies, demonstrating blunted hormonal responses to serotonergic stimuli, from studies of the levels of 5-HT metabolites in postmortem tissue and cerebrospinal fluid (CSF), selective depletion studies of 5-HT in depressed patients, alterations in the 5-HT transporter and receptors in functional brain imaging studies and post-mortem tissue studies, and through study of the mechanism of action of antidepressant agents.[12]

CSF 5-HIAA Studies

A reduction in the concentration of monoamine metabolites in the CSF reflects a reduction in neuronal activity and a consequent reduction in the release of the parent monoamine. A study of 68 patients with depression found that the CSF concentration of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA), was distributed bimodally in this population.[13] One group had a concentration of 5-HIAA in the CSF similar to that measured in healthy patients, but approximately 40% had CSF levels of 5-HIAA that were greatly reduced in comparison with healthy volunteers. In this lower subgroup, there was a correlation between the concentration of 5-HIAA and the severity of depression. This finding has been confirmed in later studies and suggests that reduced availability of 5-HT, indicated by decreased 5-HIAA levels in the CSF, is related to symptoms of depression.[11]

Selective Depletion of Serotonin and Norepinephrine

Further evidence indicating that reduced levels of 5-HT are related to the development of depression is provided by the observation that depletion of 5-HT levels is associated with precipitation of symptoms of depression.[14] Thus, these symptoms result from the depletion of all monoamine stores, including 5-HT, by administration of reserpine or the reduction of central 5-HT levels by the tryptophan hydroxylase inhibitor parachlorophenylalanine. Furthermore, depletion of tryptophan (the biosynthetic precursor of 5-HT) by use of a special diet causes a rapid clinical relapse in patients in remission from depression.[14]

Alterations in Serotonin Transporter and Receptors

Following its release from nerve endings, 5-HT is rapidly transported by a reuptake system into the presynaptic nerve terminal. Considerable evidence shows that there is an alteration in this neuronal 5-HT reuptake system in depression.[12]

Inhibitors of the 5-HT reuptake system, which includes imipramine and the selective serotonin reuptake inhibitors (SSRIs), bind to a site distinct

from that for 5-HT itself and, by negative allosterism, modulate the function of the transporter.[15] The binding of such radiolabeled agents, including tritiated ([^{3}H])-imipramine or [^{3}H]-paroxetine, to the transporter is used as a marker for assessing the number of reuptake sites present. A comparison of the binding of [^{3}H]-imipramine to brain tissue obtained postmortem from healthy patients and those identified from case notes as having a history of moderate-to-severe depressive illness, showed that the number of 5-HT transporter sites was significantly decreased in the occipital cortex and hippocampus of depressed patients.[16] Similarly, the binding of [^{3}H]-imipramine was significantly reduced, by 44%, in frontal cortex obtained from suicide victims compared with the control group.[17] The reduction in the maximum number of 5-HT transporter binding sites (B_{max}) is consistent with alterations in serotonergic circuits in depression. Thus, the decline in B_{max} may indicate a reduction in the number of serotonergic terminals and/or the number of terminals expressing the reuptake site. Recent functional brain imaging studies have confirmed these earlier findings by demonstrating a reduction in 5-HT transporter sites in the midbrain raphe nuclei in drug-free patients with depression.[18]

Prior to the advent of brain-imaging techniques, the platelet provided a useful, accessible source of tissue for the study of the serotonergic system. Platelets share a common embryological origin with serotonergic neurons and, although not capable of synthesizing 5-HT, platelets have many characteristics identical to serotonergic neurons, including active 5-HT transport, 5-HT_2 receptors, and [^{3}H]-imipramine binding sites.[19,20] Similar to observations made using postmortem brain tissue, the number of [^{3}H]-imipramine binding sites was significantly reduced, by 54%, in platelets obtained from patients with depression compared with healthy controls (Figure 2).[21] This reduction in binding, confirmed in many studies,[22] has been found to be unrelated to prior use of antidepressant medication and is not evident in other psychiatric disorders, including mania, panic disorder, and Alzheimer's disease.[12]

Many effects of 5-HT, such as the regulation of mood, anxiety, and body temperature, and control of sexual function, sleep, obsessive-compulsive behavior, eating behavior, hallucinations, psychosis, and panic attack, are thought to be mediated by an interaction of 5-HT with postsynaptic 5-HT_2 receptors.[15] In patients with depression, an increased density of postsynaptic 5-HT_2 receptor binding sites has repeatedly been reported in both frontal cortex and platelets. The density of these receptors decreases during treatment with antidepressants—an effect that coincides temporally with the clinical improvement of patients' symptoms.[12] It is therefore possible that these changes reflect an upregulation of 5-HT_2 receptors as an adap-

tive response to reductions in synaptic 5-HT concentration, which is reversed when 5-HT levels are returned to normal during antidepressant treatment.

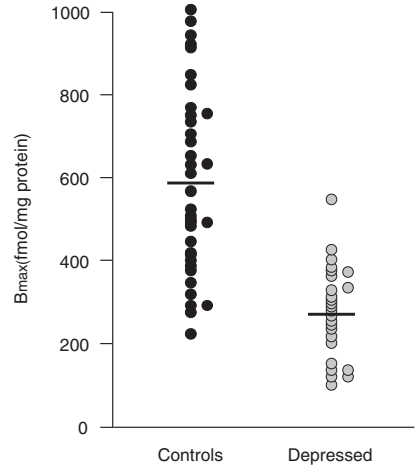
Mechanism of Action of Antidepressants

One convincing piece of evidence supporting a role for serotonergic circuit dysfunction in the development of major depression is the observation that all of the SSRIs thus far tested are effective antidepressants.[12,23] Blockade of 5-HT reuptake appears to be the only likely common mechanism of action because these agents are members of diverse chemical classes.[23] However, like all antidepressants, SSRIs inhibit 5-HT reuptake immediately following administration, but this therapeutic activity is not apparent until at least 2 weeks after commencing treatment.[15] This has led to the hypothesis that reuptake inhibition is a necessary first step that results in longer-term adaptive changes that eventually lead to persistent enhancement of serotonergic neurotransmission.[23]

The adaptive changes that occur during antidepressant therapy have been suggested to involve progressive desensitization of somatodendritic 5-HT_{1A} autoreceptors and terminal 5-HT_{1D} autoreceptors.[23] Following SSRI administration, an initial rise in extracellular 5-HT concentration results in an attenuation of neuronal firing through activation of somatodendritic 5-HT_{1A} receptors. A progressive recovery of the firing activity of these 5-HT neurons ensues, which temporarily

FIGURE 2

THE BINDING OF [^{3}H]-IMIPRAMINE TO PLATELETS OBTAINED FROM CONTROL PATIENTS WITH DEPRESSION*



* Data shown are individual determinations of B_{max} (fmol/mg protein) with the horizontal bar indicating the mean value.

Adapted from: Briley MS, Langer SZ, Raisman R, Sechter D, Zarifian E. Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. *Science*. 1980;209:303-305.

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coincides with the therapeutic efficacy of SSRIs, and is coincident with 5-HT_{1A} receptor desensitization. In addition, concomitant and progressive desensitization of the terminal 5-HT_{1D} autoreceptor has been postulated to occur. The combined effect of both somatodendritic and terminal autoreceptor desensitization is a gradual increase in the firing rate of the 5-HT neuron and perhaps in the amount of 5-HT released per impulse at the terminal. This concatenation of events results in a gradual enhancement of serotonergic neurotransmission over a period of weeks following initiation of SSRI therapy.

In addition to explaining the mechanism of action of SSRIs, adaptive changes in serotonergic neurotransmission may, in part, underlie the therapeutic effects of most or all antidepressants.[23] However, the precise mechanism(s) by which this occurs may vary between agents (Table 2). Thus, SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) result in the desensitization of both somatodendritic and terminal 5-HT autoreceptors through elevation of endogenous 5-HT levels, whereas 5-HT_{1A} receptor agonists desensitize the somatodendritic autoreceptor only by a direct action at this receptor. Monoamine oxidase inhibitors (MAOIs) also cause desensitization of the somatodendritic autoreceptor, both raising 5-HT concentrations and, indirectly, elevating NE concentrations, which then interact with α_2-adrenoceptors on the serotonergic cell body. Stimulation of these α_2-adrenoceptors causes an inhibition of 5-HT release. Sustained stimulation by the MAOI-induced rise in endogenous NE leads to desensitization of the α_2-adrenoceptors,

TABLE 2

THE EFFECTS OF DIFFERENT CLASSES OF ANTIDEPRESSANT TREATMENT ON SEROTONERGIC TRANSMISSION

	Somatodentritic 5-HT autoreceptor	Terminal 5-HT autoreceptor	Postsynaptic 5-HT autoreceptor	Net effect on 5-HT neurotransmission
TCAs	0	0	▲	▲
SSRIs	▼	▼	0	▲
SNRIs	▼	▼	0	▲
ECT	0	0	▲	▲
MAOIs	▼	0	0/▼	▲
5-HT_{1A} agonists	▼	0	0	▲

5-HT=serotonin; TCAs=tricyclic antidepressants; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin norepinephrine reuptake inhibitors; ECT=electroconvulsive therapy; MAOIs=monoamine oxidase inhibitors.
▲ =increase/sensitization.
▼ =decrease/desensitization.
0=no change.

Adapted from: Blier P, de Montigny C. Current advances and trends in the treatment of depression. *Trends Pharmacol Sci*. 1994;15:220-226.

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resulting in a withdrawal of the inhibitory effect and a consequent rise in serotonergic neuron firing. Tricyclic antidepressants (TCAs) and electroconvulsive therapy are devoid of effects on autoreceptors, but sensitize postsynaptic 5-HT receptors. The effect of psychotherapies that have been shown to be effective in the treatment of depression (eg, cognitive behavior therapy [CBT]) on the 5-HT system is unknown at present.

Norepinephrine

Noradrenergic cell bodies in the brainstem (lateral tegmental area and locus coeruleus) give rise to diverse projections to a variety of brain structures. The latter structure in the pons gives rise to 70% of the NE innervating the forebrain. The noradrenergic system is intimately involved in the mediation of stress responses. The locus coeruleus is sensitive to both external environmental stimuli and internal changes in homeostasis, and receives inputs from numerous other neurotransmitter systems, including 5-HT, opioid, γ-aminobutyric acid (GABA), corticotropin-releasing factor (CRF), DA, and glutamate, which feed back information on the state of internal homeostasis.[2] The NE released following activation of noradrenergic neurons mediates effects through interaction with α- and β-adrenoceptors, which may be present both pre- and postsynaptically.[3]

Although there is more controversy surrounding a putative role for NE system dysfunction than for 5-HT circuits in the neurobiology of depression, a number of studies have suggested that a dysfunction of NE neurons and/or changes in adrenergic receptor sensitivity may be important in the etiology of depression.[2] These studies have included assessment of NE deficiency, the consequences of NE depletion, NE turnover, NE receptor density and sensitivity, and study of the effects of antidepressants on the NE system.

Deficiency of Norepinephrine and Depression

A causal relationship between a relative NE deficiency and the symptoms of depression was first suggested on the basis that imipramine's antidepressant efficacy was related to its ability to increase NE levels.[1] The administration of reserpine, which results in a depletion of granules containing NE, is known to precipitate depression, though all monoamine stores are affected by reserpine, including 5-HT and DA. Direct evidence for a role of NE in depression is partly derived from studies of the major metabolite of NE, 3-methoxy-4-hydroxy-phenylglycol (MHPG), in the blood, urine, and CSF of patients with depression. However, after a myriad of studies, changes in MHPG levels are equivocal and suggest that NE metabolism may be decreased, increased, or unchanged in the patient whose depression is untreated. Unfortunately, to date there are no ligands that can measure the NE transporter binding by positron emission tomography or single

photon emission computed tomography imaging, nor are there ligands for α-adrenergic and β-adrenergic receptors routinely available.

Brain catecholamines can be rapidly depleted by inhibiting their synthesis with α-methyl-*p*-tyrosine (AMPT), and this technique can be used to assess the effects of NE and DA depletion on mood and on antidepressant response. Patients were chosen following evaluation of antidepressant response; those who no longer fulfilled the criteria for a current episode of major depression and had a 25-item Hamilton Rating Scale for Depression (HAM-D)[24] total score ≤15 were chosen for catecholamine depletion testing. Each patient had two challenge tests, 1 week apart. Each test included a baseline day, 2 days of either AMPT or diphenhydramine, and a fourth follow-up day. Diphenhydramine was used as a positive control to maintain the blinding of the study to mimic the sedative effects observed with AMPT. Behavioral ratings of mood were obtained twice daily, as were plasma samples for determination of MHPG and homovanillic acid (HVA), the major metabolite of DA.[14] AMPT administration produced significant (P<.001) reductions in the levels of MHPG (41%) and HVA (71%) at day 2. This reduction in MHPG and HVA is similar to that previously reported for healthy patients and psychiatric patients.[14] The effect of AMPT on HAM-D total scores was dramatic in those receiving desipramine but not fluoxetine. In four out of five patients receiving desipramine, increases in HAM-D total scores were equivalent to a full relapse of depression. The changes in HAM-D scores reflect clinically meaningful symptoms of depression.[14] In contrast, in patients receiving fluoxetine, no changes were observed in HAM-D total scores.[14] Diphenhydramine had no effect on HAM-D total scores in those receiving either desipramine or fluoxetine.[14]

The locus coeruleus of suicide victims was found to contain increases in tyrosine hydroxylase activity and an increased density of α_2-adrenergic autoreceptors, an observation also noted in rats subjected to either chronic stimulation of the locus coeruleus or NE depletion.[25] This may indicate that excessive stimulation of the locus coeruleus leads to depletion of endogenous NE and a corresponding increase in the levels of synthetic enzymes and upregulation of autoreceptors.

Norepinephrine Receptor Density/Sensitivity

A blunted growth hormone response to the α_2-adrenoceptor agonist, clonidine, is a highly consistent finding in studies of patients with depression.[26] Because the presynaptic α_2-adrenergic autoreceptor is pivotal in the control of NE release, alteration in the sensitivity and/or number of these receptors has major implications for the endogenous levels of NE.

Postsynaptic β-adrenoceptor downregulation is a well-documented phenomenon that occurs during long-term administration of some antide-

pressants, particularly those that affect NE.[2] Binding studies, both in vitro and in vivo, have revealed that chronic, but not acute, treatment with antidepressants downregulates β_1-adrenoceptors in the rat forebrain.[27] This change in β-adrenoceptor density appears to be a homeostatic response to the action of antidepressants, rather than a mechanism of action per se. Thus, it is likely that some antidepressants increase levels of endogenous NE, leading to prolonged stimulation of the β-adrenoceptor. This induces adaptation of intracellular signal transduction pathways and changes in the expression, phosphorylation, and/or subcellular distribution of the β-receptor, which manifests as the observed reduction in receptor number.

Effects of Antidepressants on the Norepinephrine System

In addition to the evidence reviewed above, it is documented that selective NE reuptake inhibitors (maprotiline, desipramine, reboxetine, etc) are effective antidepressants.[28] Moreover, there is considerable evidence that antidepressants with dual 5-HT/NE reuptake properties may be particularly effective antidepressants and anxiolytics, eg, venlafaxine, paroxetine, and duloxetine. The fact that inhibition of NE reuptake is the only common mechanism of action between these agents is indirect evidence that dysfunction in the NE system may be present in depression, and is corrected during treatment with these agents.

Interactions Between Serotonin and Norepinephrine

Although the evidence for roles of 5-HT and NE in the etiology of depression has been discussed separately, these monoamine systems are not independent but instead interact at virtually every level of the neural axis. For example, there is serotonergic innervation of the locus coeruleus, noradrenergic innervation of the raphe, and stimulation of α_2-adrenoceptors on 5-HT nerve terminals, a process which modulates 5-HT release.[3] In addition, exciting new research has revealed a potential for interaction between 5-HT and NE further down the cascade of biochemical events that is initiated following receptor activation.[9]

There is an evolving hypothesis that the pathophysiology and treatment of depression involves plasticity of neural systems.[9] Thus, depression may result when there is a failure to produce an adaptive response to stimuli such as stress. Studies of the rodent hippocampus have suggested that stress-related glucocorticoids can induce damage in CA3 pyramidal neurons and influence the rate of granule cell neurogenesis in the dentate gyrus.[9] Moreover, clinical observations have indicated that the size and function of the hippocampus is reduced in depression.[9] Preliminary evidence indicates that administration of several classes of antidepressants is associated with increased neurogen-

esis in the rodent hippocampus.[29] Thus, antidepressants could oppose the stress-induced loss of neurons either by correcting an initial dysfunction or by inducing adaptive changes directly.

Another potential mechanism of action of antidepressants in this respect may be to increase expression of brain-derived neurotrophic factor (BDNF) through upregulation of the cyclic adenosine monophosphate (cAMP) cascade.[9] For example, elevation of intracellular cAMP by NE or 5-HT, following interaction with adenylyl cyclase-linked receptors (including β-adrenoceptors and 5-HT_4, 5-HT_6, and 5-HT_7 receptors), leads to phosphorylation and activation of the cAMP-response element-binding protein (CREB). CREB is a transcription factor that regulates gene expression of a number of factors that may comprise components of the intracellular cascades and neurotrophic factors, including BDNF. An upregulation of BDNF by CREB may promote the survival and function of the neurons in the hippocampus and cortex that are susceptible to stress-induced damage and atrophy.[9] Activation of CREB can also occur through phosphorylation by other kinases, including protein kinase A and calcium-dependent protein kinases. Therefore, activation of CREB could occur via receptors (eg, 5-HT_2) that are linked to the phosphatidyl-inositol (PI) pathway or the opening of membrane calcium channels. Thus, CREB may represent a common postreceptor target of both NE and 5-HT, because NE interacts with cAMP, and 5-HT interacts with the PI pathway. Antidepressants affecting these systems may ultimately lead to the generation of neurotrophic factors that could increase cell survival, promote neurogenesis, or influence monoamine systems presynaptically (to increase neuronal function) or postsynaptically (to increase the output of target neurons), and consequently improve the symptoms of depression. This hypothesis would also explain why, despite rapid alteration of endogenous monoamine levels, the therapeutic benefit of antidepressants is not observed for approximately 2–3 weeks, during which period changes in gene expression could occur.

Dopamine

The DA system in the brain, in contrast to the 5-HT and NE circuits, comprises point-to-point topographical projections from particular cell groups to particular terminal regions. Dopaminergic neurons are organized in three main pathways: the mesolimbic-mesocortical pathway linking midbrain DA cell groups with limbic and cortical regions; the nigrostriatal pathway; and the tuberoinfundibular pathway, which comprises an intrinsic hypothalamic DA pathway, that modulates the anterior pituitary gland. Dopaminergic neurons therefore innervate brain areas associated with behavioral and physiological functions that are altered in depression (eg, the cortex, limbic structures, and pituitary gland). In addi-

tion, there is a high degree of comorbidity between depression and Parkinson's disease[30,3]—a disorder well documented to be attributable to the loss of dopaminergic neurons in the nigrostriatal pathway.

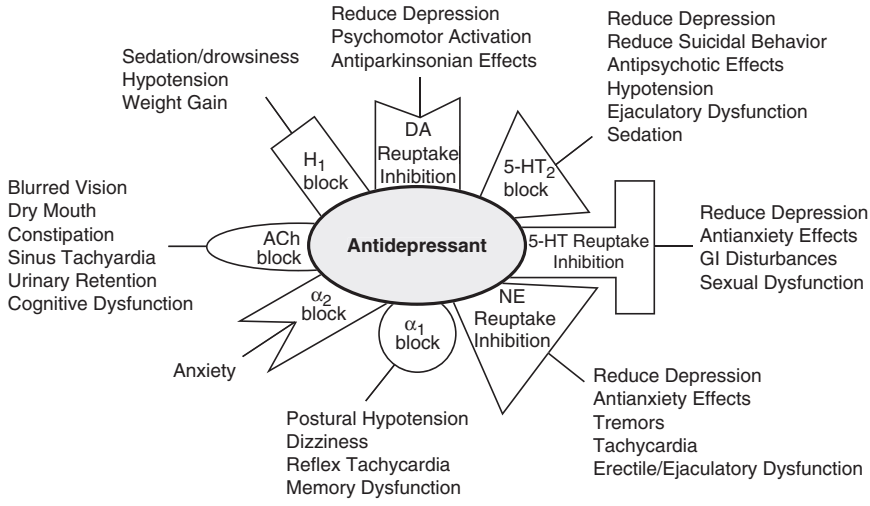
Data obtained from brain-imaging studies, postmortem tissue studies, and analyses of DA and its metabolite (HVA) in biological fluids, have all indicated that alteration of dopaminergic systems may be involved in the pathophysiology of depression.[5] Levels of HVA are reduced in patients with depression, suggesting that a decrease in DA turnover is associated with development of the disorder.[32] Furthermore, antidepressants may affect dopaminergic function. For example, DA reuptake is inhibited by some antidepressants, such as sertraline[33] and nomifensine, DA metabolism is altered during administration of MAOIs, and DA agonists such as pramipexole have antidepressant properties (Figure 3).[34]

INHIBITION OF MONOAMINE SYSTEMS BY ANTIDEPRESSANTS

The evidence evaluated supports the view that dysfunction of the 5-HT and NE systems may, at least in part, underlie the neurobiology of depression, with less evidence to support a preeminent role for DA system involvement. It is therefore reasonable to assume that an antidepressant medication that affects all three of these systems, such as a triple

FIGURE 3

THE EFFECTS OF ANTIDEPRESSANTS FOLLOWING INHIBITION OF MONOAMINE REUPTAKE SYSTEMS AND INTERACTION WITH OTHER NEUROTRANSMITTER SYSTEMS



H=histamine; DA=dopamine; 5-HT=serotonin; ACh=acetylcholine; NE=norepinephrine.

Adapted from: Richelson E. Pharmacology of antidepressants: characteristics of the ideal drug. *Mayo Clin Proc*. 1994;69:1069-1081.

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monoamine reuptake inhibitor, may offer additional benefit in the treatment of depression over a single-site agent. Such an agent would be successful only if this class of drug does not also lead to effects on other receptors, as is the case with TCAs, which are associated with additional adverse events (Figure 3). Nevertheless, if all three monoamine systems contribute to the neurobiology of depression, but the primary defect underlying the symptoms is unclear or multifactorial, the simultaneous targeting of all three systems may be advantageous. Thus, multiple-site agents may offer better efficacy.

Indeed, this may explain the apparent improved efficacy of some TCAs in comparison with SSRIs,[35,36] as well as that of venlafaxine/venlafaxine extended release, an SNRI with proven efficacy over SSRIs, in one pooled analysis.[37] Although a meta-regression analysis failed to demonstrate any difference in efficacy between dual and single reuptake inhibitors,[38] a recent meta-analysis suggests that venlafaxine has significant efficacy advantage over the SSRIs.[39] The advantage of venlafaxine over the TCAs was small and nonsignificant.

Corticotropin-Releasing Factor

The hypothalamic-pituitary-adrenal (HPA) axis is known to be activated in many patients with depression,[3] and there is considerable evidence that this is driven by hyperactivity of hypothalamic and extrahypothalamic corticotropin-releasing factor (CRF) pathways.[40-42] CRF is a hypothalamic hypophycotropic factor that controls the release of corticotropin from the anterior pituitary gland. In turn, corticotropin stimulates the adrenal cortex to release hormones essential for the organism's response to stress (glucocorticoids and mineralocorticoids). In addition to this neuroendocrine role, CRF plays a central role in coordinating the behavioral, autonomic, and immune responses to stress. Indeed, CRF is present in a variety of extrahypothalamic brain regions, for example in the locus coeruleus and amygdala,[3] which suggests a role for CRF in mood and anxiety disorders.

In one study, patients with depression were reported to have a significant twofold elevation of CRF concentration levels in CSF compared with the control group,[40] and this finding has been confirmed in several subsequent studies. In addition, there is increased expression of CRF mRNA and a fourfold increase in the number of CRF-containing neurons in the paraventricular nucleus of patients with depression compared with the matched controls.[41,42] Further analysis of these data has indicated that the number of CRF neurons showing co-localization with arginine vasopressin (AVP) was increased threefold in patients with depression, compared with those in the control group.[41] This indicates that CRF neurons are hyperactive in depression. Moreover, there are also increased numbers

of oxytocin- and AVP-containing neurons in the paraventricular nucleus of depressed patients, and oxytocin and AVP are known to modulate the HPA axis by potentiating CRF-induced corticotropin release from the pituitary gland.[43]

The observation that antidepressants modify CRF activity further supports a role for CRF in the etiology of depression. Administration of desipramine to healthy volunteers was associated with a reduction in levels of CRF in the CSF.[44] Similar findings were reported after treatment of depressed patients with fluoxetine[45] or electroconvulsive therapy.[46] Thus, antidepressants may be effective through attenuation of the hyperactivity of CRF neurons, both those that modulate the HPA axis and also extrahypothalamic CRF circuits.

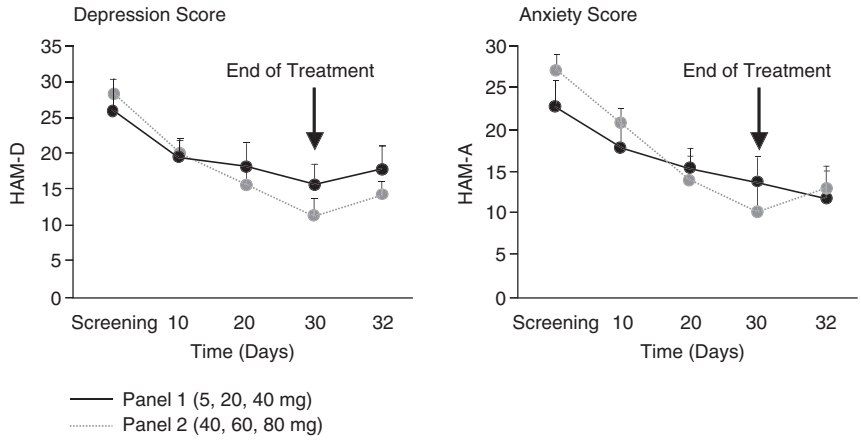
Convincing evidence of a potential role for CRF in the development of novel treatments for depression has been provided by Zobel and colleagues,[47] who reported on the effects of a CRF_1 receptor antagonist in depressed inpatients. CRF mediates its effects through interaction with CRF_1 and CRF_2 receptors, of which the CRF_1 receptor mediates stress-induced anxiety-like behavior. The experimental agent R121919 (formerly NBI30775) is an orally active and potent corticotropin-releasing hormone $(CRH)_1$ receptor antagonist. Administration of this agent to patients with severe depression was associated with a significant, dose-related decrease in HAM-D and Hamilton Rating Scale for Anxiety (HAM-A) total scores (Figure 4), indicating that antagonism of the effects of CRF was associated with antidepressant and anxiolytic activity in these patients. Symptoms of depression and anxiety returned 2 days after cessation of treatment (day 32, Figure 4), as indicated by increases in HAM-D and HAM-A total scores. Although these data show promise for antagonism of CRF as a novel mechanism of antidepressant action, R121919 is no longer a novel drug candidate due to liver toxicity. Further studies with novel CRF-receptor antagonists are underway.

Substance P

Immunoreactive substance P has been identified in at least 30 cell groups in the central nervous system, and is well documented to play an important role in pain and inflammation. In addition, substance P has been reported to play a role in mediating defensive behaviors,[48] and is co-localized with monoamines, particularly 5-HT, in limbic and spinal cord areas.[49] The possibility of a role for substance P in the neurobiology of depression has been strengthened by the observation that a substance P antagonist is active in certain models of stress, depression, and/or anxiety.[50] Moreover, administration of a substance P antagonist (MK-869) was reported to produce an antidepressant effect equivalent to that of paroxetine in patients with moderate to severe depression (Figure 5).[8] Preclinical

FIGURE 4

HAM-D AND HAM-A SCORES IN PATIENTS WITH DEPRESSION TREATED WITH THE CRF_1 RECEPTOR ANTAGONIST, R121919*



* Total scores shown were determined in patients with depression before and during 30 days of treatment with the CRF_1 receptor antagonist, R121919, at low doses (5, 20, 40 mg) or high doses (40, 60, 80 mg).

HAM-D=Hamilton Rating Scale for Depression; HAM-A=Hamilton Rating Scale for Anxiety; CRF=corticotropin-releasing factor.

Source: Zobel AW, Nickel T, Künzel HE, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatric Res*. 2000;34:171-181. Reprinted with permission from Elsevier Science.

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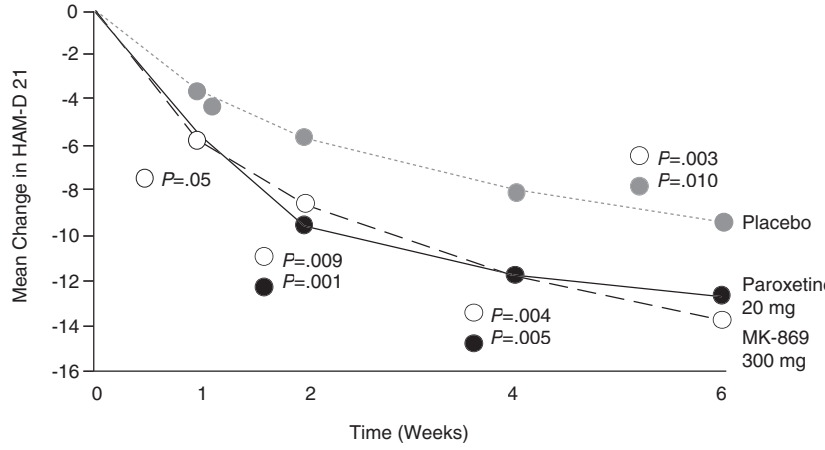
FIGURE 5

HAM-D SCORE IN PATIENTS WITH DEPRESSION TREATED WITH THE SUBSTANCE P RECEPTOR ANTAGONIST MK869, PAROXETINE, OR PLACEBO*



* Total Score shown was determined in patients with depression before and during 6 weeks of treatment with the substance P receptor antagonist MK869, paroxetine, or placebo.

HAM-D=Hamilton Rating Scale for Depression.

Adapted from: Zobel AW, Nickel T, Künzel HE, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatric Res*. 2000;34:171-181.

Nemeroff CB. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.

studies suggest that the antidepressant effect of a substance P antagonist is not mediated by augmentation of NE or 5-HT neurotransmission and, although the precise mechanism of action is at present unknown, effects of a substance P antagonist within the amygdala has been posited.[8] To date, the unequivocal efficacy of a substance P antagonist in the treatment of depression or anxiety has not yet been demonstrated, and it remains an active area of continuing investigation.

Conclusion

Evidence supports key roles for monoamines, particularly 5-HT and NE, in mediating the symptoms of depression. The neuropeptides CRF and substance P may also play cardinal roles. However, because approximately 30% of the synapses in the brain contain unidentified neurotransmitters, the possibility that other chemical messengers are involved in the pathophysiology of depression cannot be excluded.

Future research applying new and sophisticated brain-imaging techniques as well as molecular genetics will surely continue to increase our understanding of the neurobiology of depression, and have an impact on the development of novel effective treatments. Hopefully, we may be able to identify patients predisposed to depression, and moreover to identify treatment regimens with the maximum likelihood of a positive response with minimum adverse events. ✤

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Disclosure

Dr. Nemeroff is a consultant for Abbott Laboratories, Acadia Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Cephalon Pharmaceuticals, Corcept, Cypress Biosciences, Cyberonics, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Eli Lilly, Merck Inc, Mindsense, Neurocrine Biosciences, Novartis, Organon, Otsuka, Pharmacia-Upjohn, Sanofi, Scirex, Somerset, Vela Pharmaceuticals, and Wyeth. He receives grants from Abbott Laboratories, American Foundation for Suicide Prevention, AstraZeneca, Bristol-Myers Squibb, Forest Laboratories, Janssen Pharmaceutica, Eli Lilly, GlaxoSmithKline, NARSAD, National Institute of Mental Health, Pfizer Pharmaceuticals, Stanley Foundation/NAMI, and Wyeth; and he is on the Speaker's Bureau of Abbott Laboratories, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Pfizer Pharmaceuticals, and Wyeth.

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