REVIEW ARTICLE

MECHANISMS OF DISEASE

Major Depressive Disorder

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Depression is related to the normal emotions of sadness and bereavement, but it does not remit when the external cause of these emotions dissipates, and it is disproportionate to their cause. Classic severe states of depression often have no external precipitating cause. It is difficult, however, to draw clear distinctions between depressions with and those without psychosocial precipitating events.[1] The diagnosis of major depressive disorder requires a distinct change of mood, characterized by sadness or irritability and accompanied by at least several psychophysiological changes, such as disturbances in sleep, appetite, or sexual desire; constipation; loss of the ability to experience pleasure in work or with friends; crying; suicidal thoughts; and slowing of speech and action. These changes must last a minimum of 2 weeks and interfere considerably with work and family relations. On the basis of this broad definition, the lifetime incidence of depression in the United States is more than 12% in men and 20% in women.[2] Some have advocated a much narrower definition of severe depression, which they call melancholia or vital depression.[3]

A small percentage of patients with major depression have had or will have manic episodes consisting of hyperactivity, euphoria, and an increase in pleasure seeking. Although some pathogenetic mechanisms in these cases and in cases of major depressive disorder overlap, a history of mania defines a distinct illness termed bipolar disorder.[4]

Depression is a heterogeneous disorder with a highly variable course, an inconsistent response to treatment, and no established mechanism. This review presents the major current approaches to understanding the biologic mechanisms of major depression.

GENETICS

Studies comparing concordance rates for major depression between monozygotic and dizygotic twins suggest a heritability of about 37%,[5] which is much lower than the heritability of bipolar disorder or schizophrenia. Some aspects of the normal personality, such as avoidance of harm, anxiousness, and pessimism, are also partly heritable.[6] Kendler et al.[7] showed that although depression is due in part to heritable depression-prone personality traits, it is also the result of heritable factors that are independent of personality. Early-onset, severe, and recurrent depression may have a higher heritability than other forms of depression.[8] It is clear from studies of families that major depression is not caused by any single gene but is a disease with complex genetic features. Studies of pedigrees with multiple cases of major depression have identified chromosomal regions with linkage to the disorder, and some of these loci have been replicated in more than one study, although no single chromosomal region has been replicated in every family study of genetic linkage in depression. Holmans et al.[9] found

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evidence of linkage of recurrent, early-onset depression to chromosome 15q25-q26, but the population attributable risk was small.

No specific molecular risk factor has been reliably identified. One common polymorphic variant of the serotonin-transporter–linked polymorphic region (5-*HTTLPR*), which affects the promoter of the serotonin-transporter gene, causes reduced uptake of the neurotransmitter serotonin into the presynaptic cells in the brain.[10] Some studies have shown that this polymorphism confers a predisposition to depression,[11] but it also confers a predisposition to an anxious and pessimistic personality.[10] Brain imaging reveals functional differences in emotion-related areas of the brain among carriers of the different common polymorphisms of 5-*HTTLPR*,[12] although a direct relation to depression is unclear. In a large, prospective epidemiologic study, Caspi et al.[13] found that 5-*HTTLPR* predicted depression only in association with defined life stresses. Some environmental factors could confer a predisposition to depression by affecting the genome epigenetically — for example, increased maternal care in rodents causes an epigenetic change in the promoter region of the glucocorticoid-receptor gene.[14]

THE MONOAMINE-DEFICIENCY HYPOTHESIS

The noradrenergic and serotonergic systems originate deep in the brain and fan out over almost the entire brain, suggesting a system capable of modulating many areas of feeling, thinking, and behaving. The early antidepressants blocked the reuptake of norepinephrine and serotonin by the presynaptic neuron. The immediate effects of this pharmacologic action are to increase the availability of norepinephrine and serotonin in the synapse and to increase stimulation of the postsynaptic neuron. Inhibitors of the enzyme monoamine oxidase were also discovered to have antidepressant properties. This enzyme catabolizes norepinephrine and serotonin in their respective presynaptic neurons, and such inhibition could be expected to increase the availability of neurotransmitters. These discoveries led to a major theory of depression known as the monoamine-deficiency hypothesis. Numerous studies of norepinephrine and serotonin metabolites in plasma, urine, and cerebrospinal fluid, as well as postmortem studies of the brains of patients with depression, have yet to identify the purported deficiency reliably. However, a newly discovered form of the enzyme tryptophan hydroxylase, designated TPH-2, is specific to the brain[15] and could explain why previous postmortem studies of total enzyme activity did not show differences in tryptophan hydroxylase activity between patients with depression and controls.[16] A recent positron-emission tomographic study using a ligand for brain monoamine oxidase showed a 30% increase of the enzyme in a subgroup of patients with depression.[17] A study measuring differences in monoamine metabolites between the internal jugular vein and the brachial artery showed lower production by the brain of norepinephrine metabolites in patients with depression than in controls.[18] The monoamine-deficiency hypothesis continues to stimulate research whenever a new technical window into the brain is opened.

Serotonin and norepinephrine can be depleted experimentally in humans by oral treatments.[19] A drink containing all amino acids except tryptophan stimulates the liver to synthesize proteins and rapidly depletes the plasma (and therefore the brain) of tryptophan. Tryptophan is rate-limiting for serotonin synthesis in the brain. Such oral tryptophan depletion does not induce depression in healthy subjects but will cause a relapse of depression in patients who have been successfully treated with a serotonin-reuptake inhibitor.[19] Similarly, α-methyl paratyrosine inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. Treatment with α-methyl paratyrosine does not induce depression in normal subjects but will induce a relapse in patients who have been treated successfully with a norepinephrine-reuptake inhibitor.[19] These findings suggest that norepinephrine and serotonin have critical roles in the mechanisms of these treatments of depression but that additional neurochemical factors are necessary to cause depression.

Because direct measurements of monoamine neurotransmission did not yield definitive findings in relation to depression, the downstream effects of monoamine neurotransmission were explored (Fig. 1). The serotonin-1B receptor is located presynaptically and regulates the release of serotonin by feedback inhibition. Postmortem studies show that the levels of p11, a protein that enhances the efficiency of serotonin-1B receptor signaling, are decreased in the brains of patients with depression.[20] The serotonin-1A receptor is located both presynaptically and postsynaptically to regulate

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serotonin function (Fig. 1). The receptor can be evaluated in patients with depression by injecting specific agonists and measuring specific neuroendocrine responses, such as elevation of the prolactin level.[21] Results suggest that the sensitivity of this receptor is reduced in patients with depression.[21] The α_2-noradrenergic receptor, which is usually presynaptic, modulates norepinephrine release by feedback inhibition (Fig. 1). Heightened receptor sensitivity has been described in patients with depression,[22] which is consistent with reduced norepinephrine release.

It is conceivable that the second-messenger systems for serotonergic and noradrenergic neurotransmission malfunction in depression, and for this reason the phosphatidylinositol and cyclic AMP second-messenger systems have been extensively evaluated. Reduced inositol levels have been found in postmortem studies of the brains of persons who have died by suicide[23] and in magnetic resonance spectroscopic studies of the frontal cortex in patients with depression.[24] A blunted cyclic AMP response to stimulation was found in postmortem studies of the brains of patients with depression.[25] These reductions in second-messenger function may impair neurotransmitter function even without changes in monoamine levels or receptor numbers. These data indirectly support elaborations of the original monoamine-deficiency hypothesis of depression (Fig. 1).

G proteins that mediate signaling between receptors and second-messenger systems have also been investigated in patients with depression, both in postmortem studies of the brain[26] and in studies of peripheral-blood cells.[27] Although these systems are clearly affected, no consistent picture has emerged because there are numerous forms of G proteins that vary in different areas of the brain. The cyclic AMP response element–binding protein (CREB) is a transcription factor affected by cyclic AMP in the cell. In an animal model of depression, rats with overexpression of CREB in the dentate gyrus behaved similarly to rats treated with antidepressants, but the opposite effect was found when CREB was overexpressed in the nucleus accumbens.[26,28] Thus, the role of CREB in depression is specific to the region of the brain. Most but not all studies show that long-term treatment with antidepressants stimulates CREB function, possibly depending on the type of drug and the dosage.[28] Levels of CREB and phospho-CREB were reduced in postmortem studies of the cortexes of patients who had a major depressive disorder and had not taken antidepressants, as compared with controls.[26,28] Many studies of second-messenger systems and transcription factors in depression were inspired by the belief that it takes several weeks before antidepressant treatment has an effect; consequently, the studies were designed to detect time-dependent biochemical changes in the cell. New meta-analyses suggest that antidepressant effects begin rapidly, however,[29] thereby supporting the classic monoamine-deficiency hypothesis.

A strong point of the monoamine theory has been its predictive power. Almost every compound that has been synthesized for the purpose of inhibiting norepinephrine or serotonin reuptake has been proved to be a clinically effective antidepressant. A behavioral model of depression has been developed in which a rodent is placed in a glass cylinder filled with water, the sheer wall offering no chance of escape. The animal struggles for a while and then floats passively (the forced swim test). A single prior injection of antidepressant increases the struggling time; results in this model have excellent predictive validity for new antidepressants. Other animal models have been developed by selective breeding of rats for depression-like behavior, and these genetically susceptible rodents also have a response to antidepressants.[30] Still other models that can be studied biochemically induce depression with the use of long-term mild stress or learned helplessness. However, no animal model of depression captures the periodic change of behavior into and out of depression that is seen in patients with depression.

Molecular techniques such as gene knockout partially support the monoamine theory of depression. The serotonin-reuptake–transporter knockout mouse is excessively anxious and characterized by increased immobility in the forced swim test.[31] This effect is similar to that of the low-activity polymorphic variant of the serotonin receptor on human personality[10] but is the opposite of the expected effects of serotonin-reuptake–inhibitor antidepressants. However, this inconsistency could be explained by the difference between a chronic monoamine abnormality during brain development[31] and the hypothesized acute monoamine depletion in an adult with depression. Table 1 shows the effects in mice of knocking out genes related to monoamine neurotransmitters.

The effects of stimulants on mood indirectly

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support the monoamine-deficiency hypothesis of depression and show that mood can be altered rapidly. Cocaine and amphetamines are powerful releasers of monoamines into the synapse as well as inhibitors of reuptake. Their mood-elevating effects are immediate, but in patients with severe depression they have often been reported to cause agitation rather than relief of depression. This finding could reflect the ability of these stimulants to deplete the presynapse of monoamines and thus cause a "crash" into depression. Recent studies support the theory that an acute response to a single dose of amphetamine predicts a patient's longer-term response to monoamine-reuptake inhibitors.[46]

The role of dopamine deficiency in depression is suggested by the frequency of depression in patients with Parkinson's disease and the effect of reserpine, which depletes serotonin, norepinephrine, and dopamine, causing a hypoactive state in animals. The antidepressant agent buproprion inhibits the reuptake of dopamine. Some direct dopamine-receptor agonists, such as pramipexole, have been reported to be efficacious in the treatment of depression, even though they were developed for Parkinson's disease.[47]

A major liability of the monoamine-deficiency hypothesis is its derivation from the mechanism of currently available antidepressants. Approximately two thirds of patients have a clinical response to these agents, whereas one third have a response to placebo.[48] Perhaps the mechanism of depression is not related to monoamines in two of three cases.

Figure 1 (facing page). The Monoamine-Deficiency Hypothesis Extended.

The monoamine hypothesis of depression postulates a deficiency in serotonin or norepinephrine neurotransmission in the brain. Monoaminergic neurotransmission is mediated by serotonin (5-hydroxytryptamine 1A [5-HT1A] and 5-hydroxytryptamine 1B [5-HT1B]) or norepinephrine (noradrenaline) released from presynaptic neurons (serotonergic neuron, shown on the left side, and noradrenergic neuron, shown on the right side [condensed virtually]). Serotonin is synthesized from tryptophan, with the first step in the synthetic pathway catalyzed by tryptophan hydroxylase; norepinephrine is synthesized from tyrosine, with the first step catalyzed by tyrosine hydroxylase. Both monoamine transmitters are stored in vesicles in the presynaptic neuron and released into the synaptic cleft, thereby affecting both presynaptic and postsynaptic neurons. Cessation of the synaptic action of the neurotransmitters occurs by means of both reuptake through the specific serotonin and norepinephrine transporters and feedback control of release through the presynaptic 5-HT1A and 5-HT1B regulatory autoreceptors for serotonin and the α2-noradrenergic autoreceptors for norepinephrine. Monoamine oxidase A (MAO-A) catabolizes monoamines presynaptically and thereby indirectly regulates vesicular content. The protein p11, which interacts with 5-HT1B receptors, increases their function. Postsynaptically, both serotonin and norepinephrine bind two kinds of guanine nucleotide triphosphate–binding protein (G protein)–coupled receptors: cyclic AMP (cAMP)–coupled receptors, which activate adenylate cyclase (AC) to generate cAMP, and phosphatidylinositol (PI)–coupled receptors, which activate phospholipase C (PLC). PLC generates inositol triphosphate (IP_3) and diacylglycerol (DAG); cAMP activates protein kinase A (PKA), and IP_3 and DAG activate protein kinase C (PKC). The two protein kinases affect the cAMP response element–binding protein (CREB). Findings in patients with depression that support the monoamine-deficiency hypothesis include a relapse of depression with inhibition of tyrosine hydroxylase or depletion of dietary tryptophan, an increased frequency of a mutation affecting the brain-specific form of tryptophan hydroxylase (TPH-2), increased specific ligand binding to MAO-A, subsensitive 5-HT1A receptors, malfunctioning 5-HT1B receptors, decreased levels of p11, polymorphisms of the serotonin-reuptake transporter associated with depression, an inadequate response of G proteins to neurotransmitter signals, and reduced levels of cAMP, inositol, and CREB in postmortem brains.

STRESS, THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS, AND GROWTH FACTORS

Stress[49] is perceived by the cortex of the brain and transmitted to the hypothalamus, where corticotropin-releasing hormone (CRH) is released onto pituitary receptors. This stimulus results in the secretion of corticotropin into plasma, stimulation of corticotropin receptors in the adrenal cortex, and release of cortisol into the blood. Hypothalamic cortisol receptors respond by decreasing CRH production to maintain homeostasis (Fig. 2).

There is considerable evidence that cortisol and its central releasing factor, CRH, are involved in depression.[50,51] Patients with depression may have elevated cortisol levels in plasma,[38] elevated CRH levels in cerebrospinal fluid,[50] and increased levels of CRH messenger RNA and protein in limbic brain regions.[50] In studies using dexamethasone to evaluate the sensitivity of the hypothalamus to feedback signals for the shutdown of CRH release, the normal cortisol-suppression response is absent in about half of the most se-

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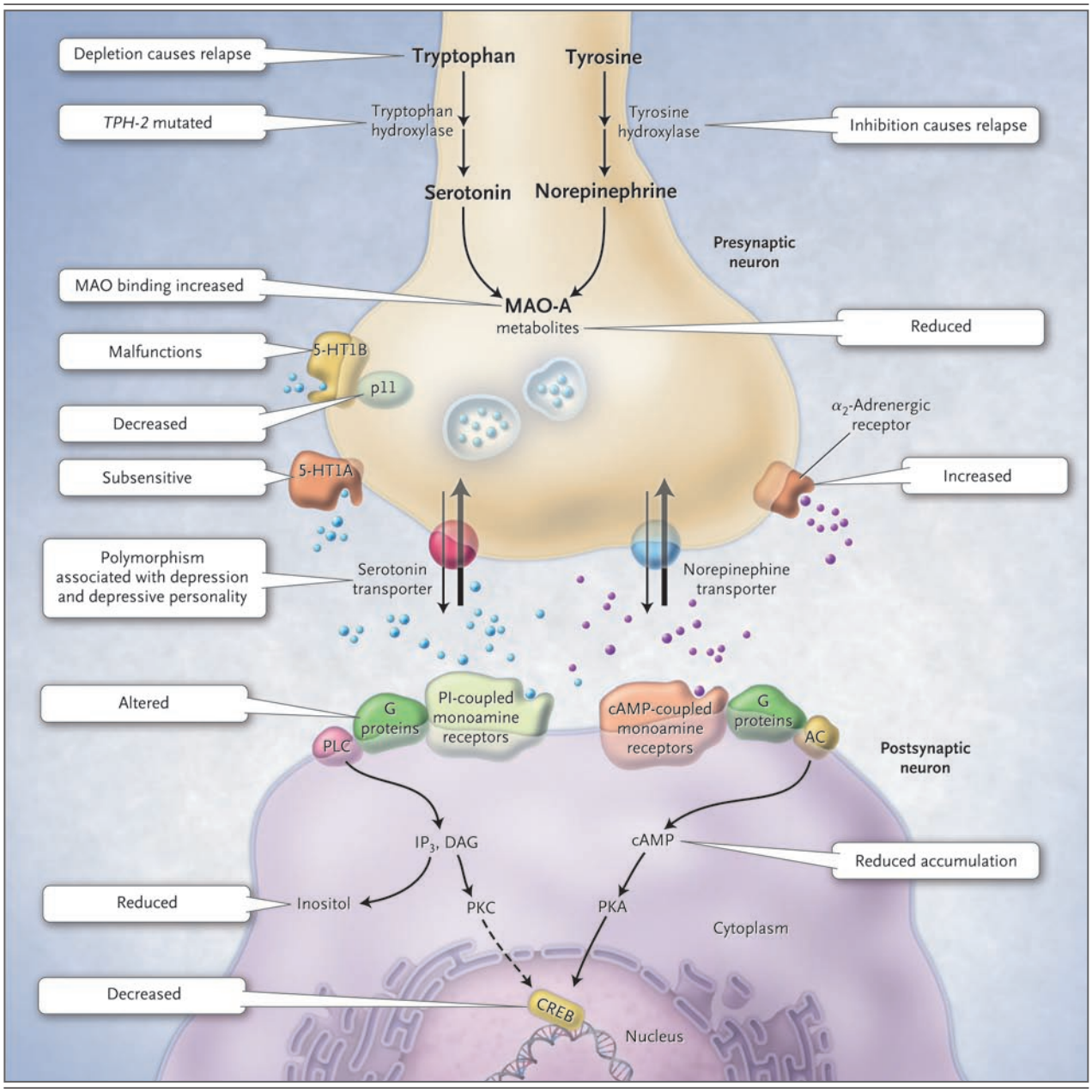

verely depressed patients.[52] Antidepressant-induced clinical remission is accompanied by reversal of some of these abnormalities.[52]

Adults with a history of physical or sexual abuse as children have increased levels of CRH in cerebrospinal fluid.[53] Adult rodents that were separated from their mothers or abused as pups show increased immobility in the forced swim test, which is reversed by antidepressant treatment.[54] Mice with region-specific knockout of the glucocorticoid receptor at an adult age have increased activity of the hypothalamic–pituitary–adrenal axis and increased immobility in the forced swim test, both of which are reversed by antidepressants.[55] Increased levels of monoamines in the synapse affect the hypothalamic–pituitary–adrenal axis[56] and reverse some of the long-term effects of stress.[56] It is possible that antidepressants relieve depression by reducing the secondary stress caused by a painfully dispirited mood rather than by directly elevating mood. An antistress mechanism could explain the general usefulness of antidepres-

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Table 1. Monoamine-Related Gene Knockouts That Affect Depression-Related Behavior in Mice.*

Gene or Protein	Function	Depression-Related Changes	Corroboration of Monoamine-Deficiency Hypothesis	Other Behavior Elicited by Knockout of Gene
sert	Serotonin transporter	Increased depressive behavior, reduced serotonin level, desensitized postsynaptic 5-HT1AR, and reduced presynaptic 5-HT1AR function[32]	No	Excessive anxiety[32]
net	Norepinephrine transporter	Reduced depressive behavior, prolonged norepinephrine clearance, elevated extracellular norepinephrine levels[33]	Yes	Increased locomotion response to amphetamines and cocaine[33]
5-ht1ar	Serotonergic 1A receptor (presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior, normal serotonin level and release, impaired SSRI-induced neurogenesis[32]	No	Excessive anxiety, impaired hippocampal learning[32]
5-ht1br	Serotonergic 1B receptor (presynaptic autoreceptor and postsynaptic)	Reduced response to SSRI in forced swim test, reduced serotonin level and increased serotonin release, increased SSRI-induced serotonin release, decreased serotonin-transporter expression[32]	Yes	Increased aggressiveness, reduced anxiety, increased exploration, increased use of cocaine[32]
p11 (protein)	Interacts with and enhances signaling efficiency of 5-HT1BR	Increased depressive behavior, increased serotonin turnover[20]	No	Not reported[20]
5-ht2ar	Serotonergic 2A receptor	No change[34]	No	Reduced inhibition in conflict-anxiety paradigms[34]
5-ht7	Serotonergic 7 receptor (possibly presynaptic autoreceptor and postsynaptic)	Reduced depressive behavior and REM sleep duration[35]	No	Normal locomotion[35]
α_{2a}*ar*	α_{2A}-Adrenergic receptors (presynaptic autoreceptor)	Reduced norepinephrine levels, presynaptic inhibition of release,[36] increased depressive behavior[37]	No	Altered sympathetic regulation,[36] impaired motor coordination
α_{2c}*ar*	α_{2C}-Adrenergic receptors (presynaptic autoreceptor restricted to central nervous system)	Reduced depressive behavior[38]	Yes	Increased aggressiveness,[32] increased locomotion response to amphetamines[36]
mao-a	Monoamine oxidase A	Increased brain serotonin and epinephrine levels[39]	No	Increased aggressiveness and response to stress,[30] decreased exploration[32]
ac VII (heterozygotes)	Adenylyl cyclase type 7	Reduced depressive behavior[40]	No	Unchanged anxiety[40]
impa1	Inositol monophosphatase 1	Reduced depressive behavior, unaltered brain inositol levels[41]	Yes	Increased hyperactivity and sensitivity to pilocarpine-induced seizures[41]
smit1	Sodium-*myo*-inositol transporter 1	Reduced depressive behavior and brain inositol levels[42]	Yes	Increased sensitivity to pilocarpine-induced seizures[42]
creb	Cyclic AMP–response element–binding protein	Reduced depressive behavior, normal antidepressant-induced behavior[43]	No	No increase in BDNF after long-term use of antidepressants[43]
bdnf				
Male mice	Brain-derived neurotrophic factor	No depressive behavior[44]	No	Increased aggressiveness, hyperphagia,[45] hyperactivity[44]
Female mice	Brain-derived neurotrophic factor	Increased depressive behavior[44]	Yes	Increased aggressiveness, hyperphagia[45]

* BDNF denotes brain-derived neurotrophic factor, 5-HT1AR 5-hydroxytryptamine 1A receptor, 5-HT1BR 5-hydroxytryptamine 1B receptor, REM rapid eye movement, and SSRI selective serotonin-reuptake inhibitor.

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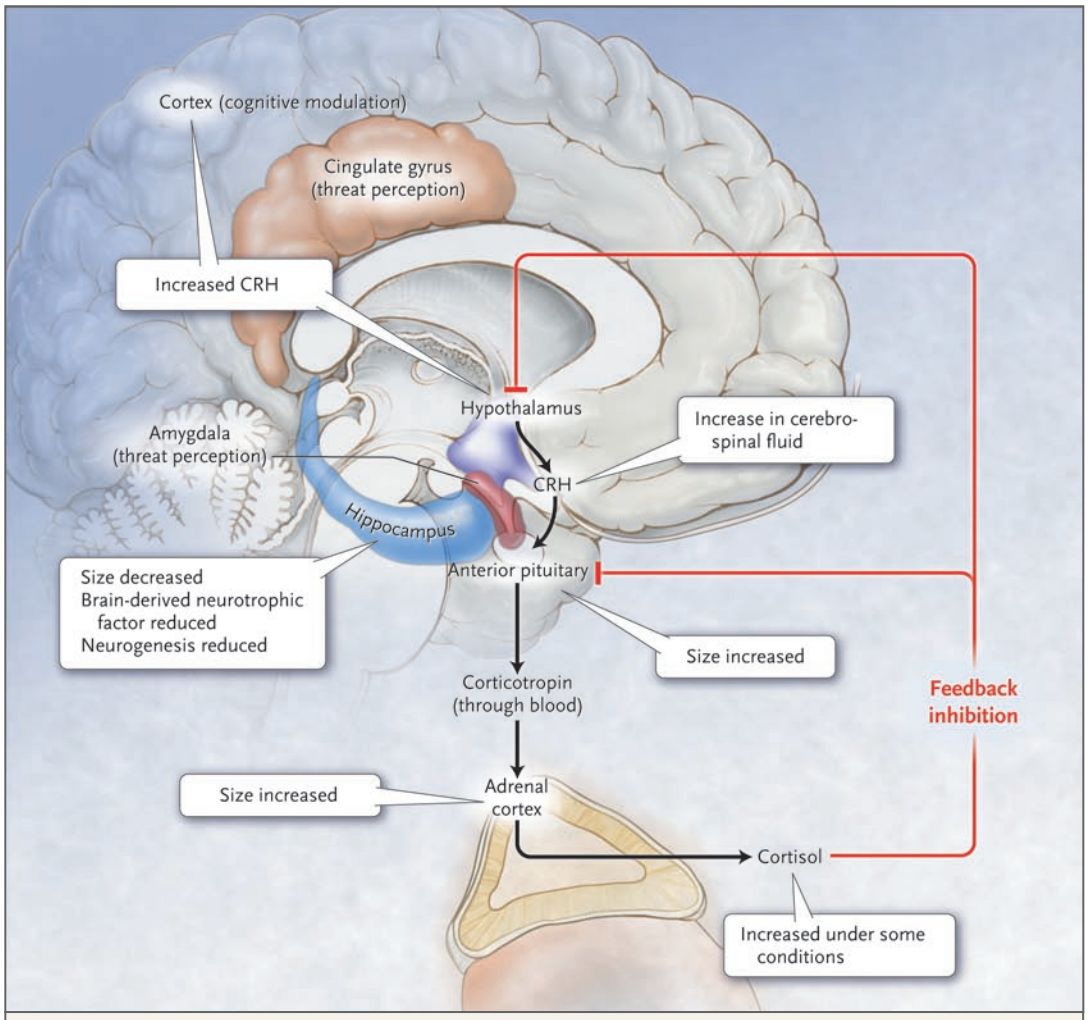

Figure 2. The Hypothalamic–Pituitary–Cortisol System in Depression.

The hypothalamic–pituitary–cortisol hypothesis of depression postulates that abnormalities in the cortisol response to stress may underlie depression. The black arrows show that in response to stress, which is perceived by the brain cortex and the amygdala and transmitted to the hypothalamus, corticotropin-releasing hormone (CRH) is released, inducing the anterior pituitary gland to secrete corticotropin into the bloodstream. Corticotropin stimulates the adrenal cortexes to secrete the glucocorticoid hormone cortisol. The red lines show that cortisol, in turn, induces feedback inhibition in the hypothalamus and the pituitary, suppressing the production of CRH and corticotropin, respectively. Findings in patients with depression that support the hypothalamic–pituitary–cortisol hypothesis include the following: cortisol levels are sometimes increased in severe depression, the size of the anterior pituitary and adrenal cortex is increased, and CRH levels in the cerebrospinal fluid and CRH expression in the limbic brain regions are increased. Hippocampal size and the numbers of neurons and glia are decreased, possibly reflecting reduced neurogenesis due to elevated cortisol levels or due to reduced brain-derived neurotrophic factor.

sants for a wide variety of psychiatric conditions, including panic disorder, post-traumatic stress disorder, bulimia, premenstrual syndrome, and obsessive–compulsive disorder. CRH-receptor antagonists show antidepressant activity in animal models,[57] but the results of large clinical trials have been disappointing. A compound that blocks the glucocorticoid receptor has been reported to be efficacious in depression, but only the most severe and psychotic type.[58]

A single test for the cortisol level in blood does not contribute to the diagnosis of depression, since levels of cortisol vary markedly in a circadian rhythm[38] and because the overlap between values in patients and those in controls is considerable. Mild stress induced in the laboratory, such as

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Table 2. Additional Biologic Theories of the Pathophysiology of Depression.*

Theory	Supporting Evidence	Contradictory Evidence
Altered glutamatergic neurotransmission	Glutamate and glutamine levels in the prefrontal cortex are reduced[91]	Glutamate levels in the occipital cortex are increased[92,93]
	Intravenous ketamine, an NMDA antagonist, induces rapid, sustained antidepressant effect [94]	Ketamine binds to high-affinity-state D2 dopamine receptors[95]
	Cortical messenger RNA levels of glutamate transporters and of the enzyme that converts glutamate to glutamine are reduced[96]	It is not clear whether antidepressants affect AMPA receptors in the brain[97]
Reduced GABAergic neurotransmission	Levels of GABA in plasma, cerebrospinal fluid, the dorsolateral prefrontal cortex, and the occipital cortex are reduced[91-93]	GABA occurs in more than 30% of brain synapses, suggesting nonspecificity
	GABA-modulating agents have effects in animal models of depression[98]	There is a lack of difference in prefrontal cortex GABA levels on MRS in depression[99]
	Antidepressants affect GABAergic function[98]	GABA neurotransmission may be related to symptoms of anxiety in depression
	GABA neuron immunoreactivity is reduced in the prefrontal cortex[100]	
Abnormal circadian rhythms	Sleep deprivation and light therapy have antidepressant effects[101,102]	The association between clock-related genes and depression is inconsistent[103]
	Some patients with depression have circadian abnormalities of mood, sleep, temperature, and neuroendocrine secretion[104]	
	Rodents active during the day become depressed when daylight is shortened[105]	
Deficient neurosteroid synthesis	Cholesterol levels are low in plasma and the brain during depression[106]	The findings in schizophrenia are similar[107]
	DHEA has antidepressant effects in patients with depression[108]	Neurosteroids (neuroactive steroids in the brain that modulate neurotransmitter receptors) mostly affect memory and sleep
Impaired endogenous opioid function	δ-Opioid–receptor agonists have antidepressant-like effects in rodents and up-regulate levels of BDNF in the brain[109]	Although early reports suggested that opiates may be effective in treating depression,[110] data from large, controlled, randomized trials are lacking
	Capacity for cortical μ-opioid–receptor binding is decreased in response to sustained sadness[111]	
Monoamine–acetylcholine imbalance	Depressed mood can be induced in humans by administration of physostigmine, an acetylcholinesterase inhibitor[112]	Mecamylamine, a nicotinic acetylcholine receptor antagonist, reduced symptoms of depression[113]
	Nicotinic acetylcholine receptor antagonists potentiate antidepressants[114]	Many antidepressants are not anticholinergic
Cytokine-mediated crosstalk between the immune system and the brain	Depression is common in infectious and autoimmune diseases[115]	Most studies are correlative[116]
	Exposure to cytokines induces depressive symptoms, and cytokine secretion is increased in major depression[115]	Cytokine-induced depressive symptoms are temporary and not replicated in all studies[117]
	Antidepressants have antiinflammatory effects[115]	Substance P antagonists are not therapeutic in depression
	Cytokines affect the hypothalamic–pituitary–adrenal axis and monoamines[115]	

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Thyroxine abnormalities	Levels of transthyretin are reduced in the cerebrospinal fluid in patients with depression[118]
	Thyroid hormones modulate the serotonergic system in the brain[119]
	Thyroxine monotherapy is ineffective
	Brain neurogenesis is decreased after the administration of thyroxine in adult rats with hypothyroidism[120]
	Hypothyroidism is not manifested in most patients with depression
	Rate of response to triiodothyronine is increased during depression[121]
Dysfunction of specific brain structures and circuits	Transcranial magnetic stimulation of the prefrontal cortex[122] and deep-brain stimulation of the anterior cingulate affect mood[123]
	Implicated brain areas differ from study to study
	Glucose use is reduced in the prefrontal cortex[124] and subgenual prefrontal cortex[125]
	Inconsistent findings with respect to blood flow, volumetric, glucose utilization, and postmortem methodologies[63,124,126]
	Circuit dynamics in the hippocampus are altered in a rat model of depression[127]

* AMPA denotes alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, BDNF brain-derived neurotrophic factor, DHEA dehydroepiandrosterone, GABA γ-aminobutyric acid, MRS magnetic resonance spectroscopy, and NMDA *N*-methyl-D-aspartic acid.

stress associated with mental arithmetic calculations or simulated public speaking, results in greater changes in plasma cortisol levels than most reported differences between the values in patients with depression and those in controls.[38] It is possible that chronic mild elevations of cortisol, especially at night, when cortisol levels in normal subjects are very low, have a pathogenic role in depression. It is also possible that peripheral cortisol elevations are only a reflection of central disturbances in CRH signaling, which mediate the effects of environmental stress on mood.[59] A major liability of the hypothalamic–pituitary–adrenal axis theory of depression is the difficulty of defining the relationship of stress to depression. Some patients have a single lifetime depressive episode, whereas a larger proportion have a recurrent or even chronic course. Various types of acute stress, early childhood trauma, or long-term psychosocial problems may be involved and may lead to different responses of the stress system. Stress may be causative in some cases and secondary to depressed mood in others.

Severe stress in rodents does not necessarily model the common stresses of childhood. The association of abuse in childhood with psychopathologic disorders, including depression, in adulthood could be due to common factors linking family perpetrators of abuse and their victims, including not only shared genes but also a shared environment of poverty, poor nutrition, and poor prenatal care. Depression is not uncommon in people with no psychosocial risk factors. Most patients treated for depression have no evidence of hypothalamic–pituitary–adrenal dysfunction, just as most such patients have no direct evidence of brain monoamine deficiency.

The classic teaching is that neurons do not divide in the adult mammalian brain, but studies have shown that neurogenesis occurs in several areas of the brain, especially the hippocampus. Neurogenesis is more prominent in rodents than in primates,[60] and some have questioned whether it occurs in the human cortex.[61] Elevated levels of glucocorticoids can reduce neurogenesis, and this has been suggested as a mechanism for the decreased size of the hippocampus on magnetic resonance images of the brain in many patients with depression.[62] In postmortem studies of patients with depression, cell loss in the subgenual prefrontal cortex, atrophy in the dorsolateral prefrontal cortex and the orbitofrontal cortex, and

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increased numbers of cells in the hypothalamus and the dorsal raphe nucleus have been reported.[63] These effects resemble the atrophic changes in the brain in patients with Cushing's disease[64] and in rodents treated with glucocorticoids.[65] However, cortisol elevations in depression are much lower than in Cushing's disease.

Restraint in a small container induces stress in rodents, suppressing neurogenesis, and this effect is countered by antidepressant treatment.[66] Antidepressants also enhance neurogenesis in nonhuman primates.[67] Santarelli et al.[68] irradiated the hippocampus in mice and abolished neurogenesis. They found that the radiation also abolished the ability of the animals to respond behaviorally to antidepressant treatment in the forced swim test, but this phenomenon does not occur in every mouse strain studied.[69] Henn and Vollmayr summarized other studies providing evidence that decreased neurogenesis is a result of stress and anxiety but may not be behaviorally relevant.[70] The relevance of animal models of neurogenesis to clinical studies of depression has been questioned by analogy with studies of neuroprotection strategies in stroke, for which numerous findings in animal models have not been replicated in human studies.[71]

Brain-derived neurotrophic factor (BDNF), a neurotrophic peptide, is critical for axonal growth, neuronal survival, and synaptic plasticity,[72] and its levels are affected by stress[73] and cortisol.[74] A postmortem study of patients with depression who had committed suicide showed that BDNF was reduced in the hippocampus.[75] Antidepressant drugs and electroconvulsive therapy up-regulate BDNF and other neurotrophic and growth factors[75,76]; a single bilateral infusion of BDNF into the dentate gyrus has antidepressant-like effects.[77] One study showed that the hippocampus was smaller than normal in patients with depression who carried a met166 BDNF allele.[78] In an animal model of depression, epigenetic histone methylation mediated down-regulation of *BDNF* transcripts and antidepressant treatment reversed this effect.[79] These studies suggest that BDNF is the link among stress, neurogenesis, and hippocampal atrophy in depression. However, a genetic association of the BDNF val166met polymorphism with depression has not been replicated in most studies,[74] and BDNF may be related not only to depression but to multiple psychiatric disorders.[74] BDNF-knockout mice have behaviors unrelated to depression.[45] Reduced BDNF levels in the peripheral blood of patients with depression seem to derive almost entirely from blood platelets,[80] and many artifacts must therefore be considered in interpreting these findings. Inflammation in the brain and some neurotoxins increase brain BDNF levels, suggesting that the actions of BDNF are not uniformly therapeutic.[81] Castrén[82] has proposed that antidepressant treatments may increase synaptic sprouting and allow the brain to use input from the environment more effectively to recover from depression. This hypothesis highlights the role that cognition may play in depression and suggests that biochemical mechanisms may be nonspecific.

Strong epidemiologic data point to an association between major depressive disorder and increased cardiovascular morbidity and mortality.[83] In many patients, cardiovascular disorders precede depression, and in others, depression precedes the cardiovascular disorder. Both n–3 fatty acid deficiency[84] and elevated plasma homocysteine levels[85] have been implicated in cardiovascular disease and in depression. Elevated cortisol levels in depression could increase the risk of coronary artery disease, since cortisol increases visceral fat.[64,86] Antidepressant treatment increases the survival rate among patients who become depressed after coronary occlusion.[86] Endothelial-cell signaling plays a crucial role in brain neurogenesis,[87] and these cells secrete BDNF; thus, both depression and cardiovascular disease could be examples of an endothelial disorder. Signs of inflammatory processes have been described in major depression[88] and in cardiovascular disease. Some data suggest that exercise has protective or therapeutic effects in depression.[89] Rodent models support this possibility.[90]

OTHER POSSIBLE MECHANISMS

Table 2 summarizes possible pathophysiological mechanisms of depression other than those based on the monoamine-deficiency hypothesis or the roles of stress, cortisol, and neurogenesis. Many of these other proposed mechanisms have also been implicated in psychiatric and neurologic disorders other than depression. Since the components of the brain are highly interconnected, it is not difficult to find possible integrative frameworks between two or more of the various theories. Testing the theories in a manner that can re-

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ject the null hypothesis has been more difficult. Research in depression has sometimes been sequentially imitative of dominant ideas in related fields, such as neurogenesis, glutamate neurotransmission, and nicotinic receptors, instead of progressing on its own path.

SUMMARY

It would be appealing to attempt to categorize depression in terms of monoamine-depletion forms that are perhaps related to genes coding for enzymes involved in neurotransmission and cortisol-related forms that are characterized by a more long-term course, hippocampal atrophy, and a history of psychosocial stress. However, the clinical data do not fall into such neat categories, since monoamine-based antidepressants are most effective in patients with severe depression when cortisol levels remain high after the administration of dexamethasone.

Major depressive disorder is likely to have a number of causes. Middle-aged or elderly patients presenting with depression may have a disorder related to cardiovascular disease and originating from endothelial dysfunction.[128] Patients in their late teens or early 20s who have severe depression may have important genetic risk factors and a high risk of manic episodes.[8] In patients with an anxious and depressive personality, depression may be due to genetically determined personality factors[11] or adverse childhood experiences.[129]

Avoidance of premature closure on any one scientific theory of the mechanism of depression will best serve the search for new, more effective treatments. It is likely that the pathogenesis of acute depression is different from that of recurrent or chronic depression, which is characterized by long-term declines in function and cognition. Mood can be elevated (by stimulants,[46] by brain stimulation,[123] or by ketamine[94]) or depressed (by monoamine depletion[19] in recovered patients) for short periods, but longer-term improvement may require reduction of the abnormal glucocorticoid function induced by stress or increases in brain neurotrophic factors.

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